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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1934

ORIGINAL ARTICLES.

CHRONIC CONGESTIVE SPLENOMEGALY AND ITS RELATIONSHIP TO BANTI'S DISEASE.

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When a patient is admitted to the wards of a hospital with an enormous spleen, anemia with leukopenia and perhaps a history of gastro-intestinal bleeding, the tentative diagnosis is likely to be Banti's disease. Many such cases have been treated—and with much success—by splenectomy. If, however, the patient is a confirmed alcoholic, or if further research discloses evidence of cirrhosis of the liver or some other intra-abdominal abnormality, the splenomegaly is apt to be attributed to *that*. In the resulting doubt and confusion the patient will probably lose the benefit of an operation from which he might have obtained great relief. For there is a prevalent impression that only Banti's disease (and not splenomegaly due to liver cirrhosis) should be treated by splenectomy.

Banti's disease, though frequently diagnosed in the ward, is, if Banti's right to define the disease that bears his name is respected, extremely rare on the autopsy table. Strictly adhering to Banti's classical description,[1,2] the patient must have progressed through certain definite stages, the spleen must show certain and none too perspicuous histologic changes and, above all, there must be no obvious etiologic factor. So rare are the cases that fill all of these requirements, both positive and negative, that most of them emerge from the pathologic laboratory labeled cirrhosis of the liver or perhaps classed on some other equally definite etiologic basis. And the Banti pigeon-hole remains nearly, if not quite, empty!

Waiving, for the moment, any consideration of the underlying nature and pathogenesis of Banti's disease, let us consider the clinical syndrome upon which the diagnosis must be based, before operation or, at least, before autopsy. In thus freeing our definition from any limitation on the basis of etiology, it must be realized that we are admitting many cases which are not Banti's disease at all under the definition which he gave to it. The picture includes both positive and negative aspects. On the negative side one must, by appropriate studies, have excluded such definite diseases as leukemia and aleukemia, hemolytic jaundice and certain cases of primary hypochromic anemia. On the positive side we must have, first, a large spleen, usually large enough to be palpated with ease and sometimes reaching to the umbilicus or lower. Many patients have hemorrhages from the stomach, esophagus or bowel and late in the disease ascites is common. Second, the blood will show anemia, except possibly in very early stages, usually hypochromic in type, with more or less leukopenia and frequently a mild thrombocytopenia. Third, if the spleen is removed it will show, histologically, cellular hyperplasia, fibrosis (Banti's "fibro-adenie") and generally also congestion.

The writer has adequate records of 47 cases showing this picture. All had large spleens. Gastro-intestinal hemorrhages occurred in 25. Ascites was present in 25. The blood showed more or less anemia in 44. Although in an occasional count the color-index was greater than unity, the blood picture was invariably recognized as that of "secondary" or microcytic anemia. Leukopenia was present at one or more blood examinations in 38 cases, usually in all counts where there was no complication tending to produce leukocytosis. Platelets were likewise numerically decreased in 23 of the 42 cases in which this point was noted.

Opportunity for microscopic examination of the spleen was afforded in 31 cases, as a result of operation or autopsy. Nearly all of these spleens were studied by Dr. F. B. Mallory and his assistants. The reports were almost monotonously uniform. Fibrosis was invariably present, though in varying degrees. Usually there was more or less vascular congestion. As this paper is not a pathologic study, further consideration of the histologic details will not be attempted. It need only be said that the changes found in these spleens were such as might be fully accounted for by long-continued passive congestion. A few cases of leukemia and especially of Hodgkin's disease, the clinical features of which resembled in some respects those of Banti's disease, have been excluded.

The records of these cases have been analyzed in an effort to determine what other lesions, if any, coëxisted with those already described, with an especial view to such lesions as might of themselves cause obstruction to the venous outflow of the spleen. The results are summarized in the table.

TABLE 1.—ANALYSIS OF CASES OF CHRONIC CONGESTIVE SPLENOMEGALY.

	Total.	Not operated upon.	Splenectomy.		
			Died of operation.	Relieved.	Not relieved.
Alcoholic cirrhosis	9	4	2	2	1
Toxic cirrhosis	3	1	2	..	..
Syphilitic cirrhosis	5	2	2	..	1
Cirrhosis of undetermined type	7	3	..	3	1
Non-cirrhotic liver abnormalities	2	1	..	1	..
Adhesions	5	2	1	2	..
Congenital heart abnormality	1	..	..	1	..
Ptosis of spleen	1	..	..	1	..
Etiology unknown	14	10	..	4	..
Totals	47	23	7	14	3

In 14 cases no obvious cause of portal obstruction was found. These were mostly the cases in which neither operation nor autopsy was done (Cases 1 to 10 inclusive). Perhaps they should have been omitted because, without opening the abdomen, most obstructive lesions other than the exceptional ones involving enlargement of the liver will be missed. A large liver may, of course, bear an obstructing lesion, but is less apt to do so than is the much less easily recognizable liver which is decreased in size.

Two of the 14 negative cases (Nos. 11 and 12) were operated upon; but the records are silent as to the presence or absence of abnormalities of the liver and other viscera.

Only 2 other cases failed to show some significant abnormality in addition to the splenomegaly. (See abstracts of Cases 13 and 14.) It is possible that the liver of Case 14, as in a case reported by Fox,[4] was actually diseased, although at operation it appeared to be normal. Since in neither of these cases any especial attention was paid to the condition of the portal and splenic veins, they can hardly be taken as evidence that the splenic fibrosis was the primary lesion. Unfortunately, neither the surgeon in exploring the abdomen nor the pathologist in performing an autopsy includes a careful study of these veins as a part of his regular routine.

In 24 (73%) of the remaining 33 cases, some form of cirrhosis of the liver was considered to be present, this conclusion being based on purely clinical evidence in 4 cases, on operative exploration in 9, and on microscopic examination of liver tissue in 11. Efforts to group these cirrhoses according to Mallory's classification[5] were not always successful, since several were so atypical that they could not be placed, even though the entire liver was available. However, at least three types of cirrhosis—alcoholic, toxic and syphilitic—were recognized beyond reasonable doubt.

The 9 cases of alcoholic cirrhosis (Cases 15 to 23, inclusive) included 3 diagnosed microscopically and 4 recognized at operation. One of the cases autopsied also showed hemochromatosis (Case 16) and one of those palpated at operation (Case 18) had

dense adhesions about the liver. In 8 of the entire 9 the patients gave histories of alcoholism, and the 1 that did not (Case 20) showed at operation a large and "finely irregular" liver.

The 3 cases of toxic cirrhosis (Cases 24, 25 and 26), the "healed acute yellow atrophy" of Mallory, were especially interesting. No case was accepted as belonging in this group unless the diagnosis was definitely proven by histologic examination of the liver. The writer believes that such cases are not uncommon and it is probable that some of the cirrhoses here included in the unclassified group were of this nature. They all had fibrotic spleens and clinically were quite as suggestive of Banti's disease as the others.

The 5 cases (Nos. 27 to 31 inclusive) classed as syphilitic cirrhosis offered considerable difficulty. All had positive Wassermann reactions (1 became negative after prolonged treatment). Nevertheless one may not assume that any abnormal liver in a syphilitic is syphilitic cirrhosis. However, in 2 cases (Nos. 27 and 30) the liver was examined microscopically and characteristic lesions were found. Two of the 5 cases showed, in addition to syphilis, other lesions which might have been influential in causing portal congestion—one (Case 29) had a cancer of the uterus, another (Case 27) had dense perihepatic adhesions. Case 28 may have had hemolytic jaundice, although he was definitely syphilitic and both the blood picture and the general clinical findings were characteristically of the Banti type.

Cases of syphilis with splenomegaly and anemia have been reported by Giffin.[6] It is interesting to note that, in his patients, while antisyphilitic treatment led to general improvement, it did not benefit the anemia nor did the spleens decrease in size. Splenectomy, however, did result in more or less striking improvement in the blood. The inference appears to be that the splenomegaly and the anemia were results, not of active syphilitic disease of the spleen, but rather of portal obstruction from syphilitic changes in the liver. Antisyphilitic treatment, while relieving the active disease in that organ, did not result in the disappearance of residual fibrotic changes nor the consequent interference with the flow of blood through the portal channels. But just this relief of the portal circulation was accomplished by removal of the spleen.

There were 7 cases of cirrhosis of undetermined type (Cases 32 to 38 inclusive). Marked evidence of a cirrhotic process was found in all of them, being based on autopsy material in 3, on biopsy in 1 and on palpation at operation in the others. All 3 of the cases in which the diagnosis was based on operative exploration had notably small, hard livers; in 1 (Case 35) the liver was surrounded by dense adhesions, possibly the result of acute abdominal suppurative disease; in another (Case 38) the liver was so irregular and scarred as to suggest toxic cirrhosis. Of the autopsied cases, 1 (Case 32) showed old portal thrombosis and a liver the gross appear-

ance of which suggested toxic cirrhosis; in another (Case 36) there was clean-cut portal cirrhosis; in a third (Case 33) the liver was possibly syphilitic; but in none was the pathologist able to state the type with certainty. This group is unsatisfactory only because the cases could not be classified etiologically. There is no evidence warranting the assumption that they were representatives of "true Banti's disease." Not only were the findings decidedly divergent, but in several of them, to say the least, the evidence is decidedly in favor of primary origin in the liver rather than in the spleen.

Cases 39 and 40 had enlarged livers and were classed as "non-cirrhotic liver disease." In neither was there any evidence as to the nature of the enlargement. A better classification would perhaps have been "liver abnormalities of undetermined nature."

Of the 5 cases (Nos. 41 to 45, inclusive) considered to be the results of adhesions about the portal area, the stories of all included operations for appendicitis. In Case 45 the diagnosis was presumptive. In all the patients whose abdomens were explored there were dense adhesions about the liver and generally also about the spleen. Clinically these cases did not differ from the others, except perhaps in the unusual completeness of recovery in the 2 that survived splenectomy. In addition to these cases classed as due primarily to adhesions, a number classed in other categories also had adhesions about the liver (Cases 11, 12, 18, 19, 27 and 35). To what extent the adhesions were responsible for the portal congestion it is impossible to say.

In Case 46, the only finding that could account for portal congestion was a cardiac abnormality considered to be congenital. He was greatly improved after splenectomy and the blood slowly returned to normal figures. When last heard from he was working as a janitor and boiler tender.

Finally there was 1 patient (Case 47) with marked ptosis of the spleen, which was palpated in a position so low that it was mistaken for a uterine fibroid. Although there was no pre-operative study of the blood, the spleen was fibrotic. She continued to present a mild microcytic anemia which slowly cleared. A somewhat similar case was reported by Pernet.[14]

Results of Splenectomy. Of the 47 cases upon which this paper is based, 24 were splenectomized. Seven of these died within a few days (29%). This seems unduly high. It must be remembered, however, that most of the cases were derived from the unfavorable material of a large municipal hospital. An unusually large proportion were in the more advanced stages of the disease, as shown by the fact that 11 (46%) had already had hemorrhages and 12 (50%) were ascitic. Several operations were distinctly of the last-resort type.

On the other hand, practically all of these patients had underlying lesions in organs other than the spleen, lesions which splenectomy

would rarely eradicate. Hence for most of them splenectomy was but a palliative operation. Believing it to be such, it has not always been advised in early cases where the patients were not yet materially incapacitated. This in spite of the fact that the operative mortality is most favorable in early operations. Years ago Osler,[8] speaking of splenic anemia, stressed its extreme chronicity. Some of his cases which seem closely related to the ones here reported lived in fair comfort for over a decade. This is especially true of those patients with alcoholic cirrhosis whose habits can be controlled. It is perfectly proper, then, to postpone operation until it is needed. But such a course, however advantageous to the patient, is not beneficial to one's statistics.

In a previous paper dealing with splenectomy, the writer[9] commented upon 2 patients (Cases 13 and 20 of the present report) who died of infections, in 1 probably septic endocarditis and in the other appendicitis, a few months after splenectomy. To these must now be added another (Case 14) who died of appendicitis after 2 years. A death from septicemia 2 years after splenectomy was reported by O'Donnell.[20] Such occurrences are not easy to account for. There is evidence that in rats and other animals splenectomy does increase the susceptibility to infection with Bartonella.[11] But, so far as the writer is aware, no similar increase in susceptibility to infection has been demonstrated in any other condition. It has been suggested that the anemia observed by Pearce, Krumbhaar and Frazier[10] both in dogs and man after splenectomy may be the result of infection, but there is not the slightest evidence that such is the case, either in their studies or in this series.

Of the 14 other splenectomy patients, 1 (Case 34) is reported to have died of acute nephritis 2 months after operation; 1 (Case 27) died in 16 months of hematemesis; another (Case 21) died of cerebral hemorrhage after 7 years. It is impossible to say to what extent the operations were responsible. Four patients were not heard from after leaving the hospital. The remaining 7 were reported well after periods varying up to 7 years after splenectomy.

As to the specific benefits to be anticipated from successful splenectomy, it may be said that, of those who survived operation, but 3 (Cases 18, 27 and 34) failed to show at least temporary improvement. Of 11 patients with gastro-intestinal hemorrhage, 2 died of operation, 7 were completely and 1 partially relieved of this symptom. Of 12 patients with ascites, 4 died of the operation and 5 were relieved of the symptom. Of the patients operated upon, 23 were anemic before splenectomy; of these, 7 died of the operation, 9 were more or less completely relieved of this symptom, 5 partially relieved, 1 not relieved and in 1 continued hemorrhage and repeated transfusions confused the picture. It is probable that the degree of relief was greater than these figures indicate, for the anemia often improves but slowly and the follow-up of several cases was incomplete.

The table shows the relative results of splenectomy and the relative mortality in the different groups classified etiologically. The number of cases, when thus subdivided, is too small to have much significance. The writer has the impression that the toxic cirrhosis group is particularly unpromising, while in those in which the lesion is largely mechanical and non-progressive, splenectomy seems to be especially beneficial.

Comment. Are any or all of these cases properly classed as Banti's disease? Certainly if one takes Banti's own definition as a criterion they are *not*. He clearly recognized the occurrence of secondary cirrhotic changes in the livers of many of his cases, but with equal clearness he excluded cases in which the cirrhosis was primary. While admitting his ignorance of the true underlying cause of the disease, he supposed it to originate within the spleen, a splenogenous irritant carried through the portal channels being the cause of the phlebitic and sclerotic vascular changes as well as of the cirrhosis.

In attempting to explain the present series of cases it is needless to appeal for aid to this purely hypothetic toxin. It would seem most improbable that one and the same irritating agent, whether derived from the spleen or from the alimentary tract, would result in lesions so fundamentally different from one another as acute yellow atrophy and alcoholic cirrhosis (using this term in its purely histological sense). Moreover we find exactly the same clinical picture and exactly the same splenic abnormalities resulting from such purely mechanical causes as obstructing adhesions, congenital heart disease and ptosis of the spleen—and all about equally susceptible of improvement after splenectomy.

We are forced to the conclusion that most, if not all, of these cases were not only associated with lesions interfering with the outflow of blood from the spleen, but were actually the results of such lesions. So far as the effect upon the spleen is concerned it seems to be immaterial where the obstructing lesion is located: it may be in the liver, in the splenic vein, in the portal vein above the junction or even in the heart. Apparently it must be a long-continued *chronic* obstruction, for Warthin[7] was unable to produce permanent enlargement of the spleen by ligating the splenic vein. Few cases of congestive heart failure last long enough. In 3 of the cases here recorded, symptoms followed 5 or 6 years after severe appendicitis. This would appear to be about the minimum.

There is little that is original about this concept. Warthin,[7] in 1910, and Johnston,[17] in 1931, expressed quite similar views. Many authors have described cases of alcoholic cirrhosis with splenomegaly showing close clinical resemblances to Banti's disease. Similar clinical states have been observed in syphilitic disease of the liver[6, 19] in ptosis of the spleen,[14] in primary obstructive disease of the portal vessels[7, 15, 21] and in persistence of an open umbilical vein.[18] Not a few observers have doubted the existence of such

an entity as Banti's disease and speak instead of Banti's *syndrome*. It is true that but few have been willing to come out squarely and unequivocally with this opinion. Thus, McNee,[3] criticizing Banti's later view, states that Banti's disease is merely an unusual type of "ordinary alcoholic cirrhosis, in which high portal pressure and changes in the spleen precede the onset of marked fibrotic changes in the liver." This is clear enough, but he adds that the term Banti's disease should be given up and the cases classed either as hepatic cirrhosis or as splenic anemia, thus merely substituting for Banti's disease the even more indefinite term, splenic anemia. The writer of the present paper has never seen a case conforming in all respects to Banti's requirements, but he does not on this account deny the possible existence of such a condition. He believes, however, that a more general appreciation of the fact that the symptom complex common to all of these various conditions may result from the state designated in the title of this paper will conduce to much clearer thinking.

A clue to the possible relationship between these cases and those of Banti might perhaps be obtained by study of the microscopic lesions, a study which the writer is not qualified to undertake. The specimens are preserved and it is hoped that they will be studied by someone more competent. Here it is only necessary to repeat that the changes found in these spleens were, in the opinion of the pathologist, due to long-continued passive congestion. It is perfectly conceivable that a primary vascular splenitis may occasionally occur with lesions which might produce similar clinical results from circulatory obstruction within the organ itself. Therein possibly lies the connecting link between Banti's disease and such cases as those described in this paper. But this is, at present, pure hypothesis.

That the anemia and other features of the blood picture are consequences of changes within the spleen is quite generally admitted in view of their almost uniform improvement after splenectomy. When one looks at microscopic sections of these spleens the striking feature is the increase in connective tissue. Yet when one takes into consideration the very great size of the organ he is impressed with the fact that there must also be a very considerable increase in the pulp. Perhaps there is such a thing as "hypersplenism." Or the anemia may be in some manner connected with the divergence of the portal blood, including that from the digestive tract, as well as that from the spleen, away from its normal course through the liver into the gastric, esophageal and other vicarious channels. The degree to which the portal blood may be thus diverted has been pointed out by McNee[3] and is much greater than is generally realized. In advanced cases of cirrhosis from 85 to 100% of the blood may find its way through collateral vessels. In such cases the metabolic products originating in the intestines and ordinarily carried directly to the liver can only reach the cells of that organ

by way of the much-dilated hepatic artery, after passing through the general circulation. However this may be, splenectomy relieves the blood abnormalities quite as regularly in the cases under discussion as it does in typical Banti's disease.

On the whole, this group of cases seems to be so distinct from those described by Banti—or perhaps we should say from Banti's conception of the cases he described—that it seems best to segregate them under a distinctive name. Yet the writer holds a sneaking suspicion that Banti would have classified some of the cases here described as primarily splenic, while the writer himself would have doubtless classed some of Banti's cases as primarily hepatic or portal. Banti's indefinite and confusing limitations have been commented upon by many writers—with especial clearness and force by Epplen.[12] We should not allow these and his hypothetical explanation to blind us to the fact that the clinical picture which he described has a much broader etiologic basis than he thought. Nor should we allow a patient to suffer needlessly just because we are not ignorant of the etiology of his ailment and can attribute it to a well-known cause.

It is believed that these results demonstrate that a considerable number of cases of splenic anemia dependent upon various lesions obstructing the portal blood flow may be relieved by splenectomy. At the same time the study demonstrates the futility of expecting to "cure" more than a very small proportion by this or any other means. However great and lasting the betterment may prove to be, it is only in those few cases where the obstructive lesion is confined to the spleen or the splenic vein that splenectomy gets rid of the underlying lesion. In a large majority of the cases, particularly the liver cirrhoses, the primary disease remains, and if it is of a progressive nature it goes merrily on. In cases where the underlying disease is far advanced the improvement in the blood and the partial relief of portal congestion can hardly be expected to restore the patient to a high degree of health.

The practical question concerns the choice of cases for splenectomy; and the practical answer is that we should "make the pathologic condition of the spleen and its effects on the blood the criterion" rather than the underlying cause (Mayo[13]). The physician or surgeon confronted with an actual case need not trouble himself with theoretical questions as to the nature of Banti's disease. If he has a patient showing the Banti pre-operative picture; if he has watched the patient long enough and studied him carefully enough to exclude leukemia, hemolytic jaundice, polycythemia and certain other conditions; if ordinary surgical considerations favor splenectomy; he need not hesitate to operate because he believes that the patient has alcoholic cirrhosis or some other equally definite cause of portal obstruction.

Case Abstracts. *Ages* are recorded as of the date of splenectomy or, if not operated upon, as of the first blood-examination recorded. *Blood:* "before operation" signifies the last examination preceding splenectomy and any preparatory transfusions; "after operation" signifies the maximum reached while under observation; the figures separated by dashes refer to hemoglobin per cent—red corpuscles—leukocytes. The *classification* of each case is indicated by italics.

Case 1.—F. C., male, age 44. Ill with chills in Italy at about age 5. Admitted for pneumonia. Liver 3 cm. below ribs; spleen to umbilicus; mild ascites. Blood, 93—4,472,000—3000. No operation. *Etiology unknown.*

Case 2.—F. D., male, age 27. Repeated epistaxis 1 year, distention of abdomen and hematuria 6 weeks. Marked ascites, superficial veins of abdomen distended; spleen enormous, reaching into pelvis; liver not palpable. Blood, 31—1,808,000—1850, later leukocyte counts 1600 to 3400; at times a few myelocytes. No operation. *Etiology unknown.*

Case 3.—W. G., male, age 25. Mildly alcoholic. Penile sore at 23, no secondaries. For 6 months debility, pallor and gastric distress. Severe hematemesis 6 months and again 3 days before admission. On entrance no ascites; spleen 9 cm. below ribs; liver normal. Afterward had 2 more hemorrhages and became ascitic. Blood, 32—1,982,000—2900, platelets apparently decreased. After leaving hospital he continued to require tapping and died in 5 months. No operation, no autopsy. *Etiology unknown.*

Case 4.—E. K., female, age 27. Metrorrhagia from puberty to age 25, no other hemorrhages; mass in upper abdomen for 6 years. Spleen occupies entire left abdomen, extending into pelvis and beyond midline; liver not felt; no ascites. Blood, 67—3,200,000—3800; platelets moderately decreased. Owing to the enormous size of the spleen and the patient's poor general condition operation was deferred. She did not apply for readmission. *Etiology unknown.*

Case 5.—M. M., female, age 66. Abdomen increasing in size for 2 months; hematemesis 3 days before admission. Marked ascites and moderate edema; heart absolutely irregular, systolic and doubtful diastolic murmurs; spleen 4 cm. below ribs. Blood, 20—1,500,000—24,400. The patient was moribund and died before she could be transfused. No autopsy. *Etiology unknown.*

Case 6.—S. N., male, age 13. For 5 months intermittent periods of fever, with increasing pallor. Heart normal; few râles both bases; liver palpable; spleen 4 cm. below ribs. Blood, 33—2,436,000—1300; platelets slightly decreased. No operation. No autopsy. *Etiology unknown.*

Case 7.—W. R., male, age 18. Admitted because of recent hematemesis and tarry stools. Spleen 6 cm. below ribs; liver not felt; no ascites. Blood, 27—1,600,000—5600, later 4000; platelets decreased. No operation. *Etiology unknown.*

Case 8.—M. S., female, age 54. Subject to epistaxis for 30 years, recently vomited a little blood; always more or less pallor, dyspnea and edema. Spleen from ribs to pelvis; liver not enlarged; no ascites, some edema. Blood, 64—3,888,000—1400; platelets much decreased, bleeding time prolonged. Owing to the immense size of the spleen and patient's poor condition she was considered inoperable. Severe hematemesis after 1 month, 9 months later became ascitic and edematous and died. No autopsy. *Etiology unknown.*

Case 9.—S. W., female, age 20. Patient's father died after splenectomy; his spleen showed lymphoblastoma. Pallor since age 10, recent retropharyngeal abscess; admitted shortly after severe hematemesis. Spleen to umbilicus; liver normal; no ascites; no enlarged lymph nodes. Blood, 62—3,360,000—2900; platelets decreased. Splenectomy refused. Readmitted after 6 months for hematemesis. Blood, 56—2,810,000—2950; platelets normal. Splenectomy again declined. Marrow puncture at

another hospital showed suspicion of leukemia, but patient's condition remains unchanged 2 years later. *Etiology unknown.*

CASE 10.—A. W., male, age 35. Since 25 or 30 has had gastric symptoms and has noticed tumor in left abdomen. Spleen varies in size, sometimes to pelvis. Blood, 65—4,516,000—5600; rare myelocytes. One year later, 70—3,072,000—1900; eosinophils 10.5%, rare myelocytes and numerous erythroblasts. This patient was observed for over 2 years, during which time the anemia deepened, the leukocytes varying up to 21,600; many erythroblasts and rare myelocytes (highest, 1.6%). He finally became ascitic and splenectomy was advised, but refused. *Etiology unknown.*

CASE 11.—C. B., Chinese male, age 42. Edema and abdominal distention 2 weeks. Spleen 7 cm. below ribs; liver normal; ascites. Blood, 93—6,000,000—4000; eosinophils 18%; obvious thrombocytopenia. Stool, slight amount of occult blood, no parasites. Splenectomy: condition of liver not noted; dense adhesions about spleen. Blood, after operation, 58—3,500,000—7400; platelets 72,000. Greatly improved, no return of ascites. Spleen 1050 gm., fibrotic, no leishmania. *Etiology unknown.*

CASE 12.—A. B., female, age 17. Pain in left abdomen and dysuria since minor injury 17 days before admission. Spleen to umbilicus, somewhat tender; liver normal; no ascites. Blood, 79—3,610,000—2950; platelets decreased. Pyuria. Splenectomy: spleen surrounded by dense adhesions and removed with difficulty; condition of liver not noted. Spleen fibrotic. Patient perfectly well at last note. *Etiology unknown.*

CASE 13.—E. B., male, age 17. Jaundice and anemia at age 11, followed by periods of dyspnea and pain. First seen at 14, when the spleen was 5 cm. below ribs and blood 60—3,244,000—6100; under arsenic blood improved to 76—4,152,000—6200; the spleen remaining unchanged. During 3 following years anemia slowly increased with wide fluctuations, spleen enlarged to 9 cm. below ribs; marked development of breasts and other feminine characteristics. Blood before operation 69—3,160,000—9900. Splenectomy. Marked improvement; blood in 2 months 116—5,080,000—11,600. Died of acute appendicitis 4½ months after operation. Autopsy showed general peritonitis and bronchopneumonia; liver 1425 gm., microscopically normal; marrow from central portion of shaft of femur red, many erythroblasts, apparently hyperplasia of secondary anemia. Spleen 870 gm., fibrotic, blood sinuses distinctly outlined, lymphoid nodules small and scattered. *Etiology unknown.*

CASE 14.—C. C., male, age 12. No hemorrhages. Spleen to umbilicus; liver not palpable; no ascites. Blood during 2 years preceding operation, 60 to 85—3,260,000 to 4,880,000—4600 to 8400 (once 17,600); fragility normal. Splenectomy; liver appeared normal. Spleen showed marked fibrosis. Greatly improved, "a happy and normal child" for 2 years; then died of appendicitis. *Etiology unknown.*

CASE 15.—A. L., alcoholic male, age 46. Appendectomy at 36, hematemesis during convalescence; since then repeated attacks of severe epigastric pain. Skin pigmented, possibly slight jaundice; spleen 7 cm. below ribs; liver to umbilicus; no ascites. Blood, 77—3,470,000—7000. Died 3 days after splenectomy. Autopsy showed peritonitis; spleen fibrotic and pigmented; liver, *cirrhosis* of *alcoholic* type, also some nodules suggestive of toxic cirrhosis.

CASE 16.—A. M., alcoholic male, age 58. Gastric distress and vomiting 3 years, occasional tarry stools and recent ascites (tapped). Skin pigmented; auricular fibrillation; spleen easily felt; ascites. Blood, 70—3,140,000—4800; later leukocytes varied from 2000 to 4000. Abdomen tapped several times. Patient was considered too ill for splenectomy and left hospital against advice. Readmitted, 3 weeks later, moribund. Autopsy: spleen 520 gm., congested and somewhat fibrotic; liver 890 gm.,

gross appearance suggested toxic cirrhosis, but microscopic examination showed *alcoholic cirrhosis* and hemochromatosis.

CASE 17.—H. W., alcoholic male, age 53. Dyspnea and edema 13 years; tapped for "pleurisy" 8 years ago, at which time he was told that the liver was large; jaundiced at times for 6 years. Marked jaundice; large heart with loud systolic murmur; emphysema; slight ascites; neither liver nor spleen felt. Blood, 45—3,300,000—10,000, later counts showed moderate leukopenia. Developed dullness at right base with cough and purulent expectoration. Died after severe hemorrhage, thought to be from stomach. Autopsy: small empyema at right base communicating with a bronchus, mitral and aortic valves thickened and calcified; spleen 535 gm., fibrotic; liver showed typical *alcoholic cirrhosis*.

CASE 18.—D. B., alcoholic male, age 50. Admitted for hernia. Spleen 5 cm. below ribs; liver barely felt; slight jaundice; marked ascites. Blood, 70—3,180,000—4000. Splenectomy; liver small and embedded in dense adhesions, preventing palpation. After operation blood 96—4,500,000—12,600. Patient continued to require aspiration at frequent intervals. Spleen fibrotic. *Alcoholic cirrhosis*.

CASE 19.—M. J., mildly alcoholic female, age 40. Malaria at 30; pelvic(?) operation at 33, at which time large spleen was discovered. Since then periods of abdominal distention, no hemorrhages. Progressive distention for 2 months. Moderately emaciated; marked ascites; spleen below umbilicus; liver normal. Blood, 20—1,664,000—1500; platelets decreased. Abdomen tapped twice; transfused 900 cc. Splenectomy; liver small and "hobnailed;" many adhesions. Died in 24 hours. Spleen 1025 gm., markedly congested, somewhat fibrotic. No autopsy. *Alcoholic cirrhosis*.

CASE 20.—C. K., female, age 38. Three hemorrhages from stomach in 10 months; abdomen enlarged 5 months, finally aspirated. Ascites; spleen to crest of ilium; liver not felt. Blood, 43—2,840,000—750; platelets much decreased. Splenectomy: liver large and finely irregular; spleen 23 by 15 by 5 cm., fibrotic. Much improved for a month, then after exposure to scarlet fever temperature rose to 104° F., after which chills, sweats and septic fever continued up to death 4 months from operation, apparently septic endocarditis. *Alcoholic cirrhosis*.

CASE 21.—M. W., probably alcoholic female, age 57. Repeated hematemesis and constant "stomach trouble" for 30 years. Spleen 4 cm. below ribs; liver just palpable; no ascites. Blood, 30—2,136,000—1650; slight decrease in platelets. Splenectomy: liver small and hard; slight ascites; stomach rigidly constricted (hour-glass); gall stones. Spleen fibrotic. Much improved, but continued to have occasional hemorrhages. Died of cerebral hemorrhage at 64. *Alcoholic cirrhosis*.

CASE 22.—M. M., alcoholic, female, age 53. For 4 weeks epigastric pain, hematemesis and tarry stools. Spleen 4 cm. below ribs; liver not palpable; slight ascites. Blood, 43—3,000,000—2200. *Alcoholic cirrhosis*.

CASE 23.—W. Z., alcoholic male, age 40. Hematemesis day before admission, repeated several times later with tarry stools. Ascites tapped. Loud systolic murmur at apex and aortic area; spleen 4 cm. below ribs; liver not palpable. Blood, 70—4,100,000—3800; platelets greatly decreased. No operation. *Alcoholic cirrhosis*.

CASE 24.—T. C., female, age 54. Epistaxis, but no hemorrhage from alimentary tract; jaundice 6 weeks. Spleen 6 cm. below ribs; liver not palpable; slight ascites. Blood, 60—3,620,000—2600; platelets decreased. Splenectomy: liver much contracted and coarsely lobulated. Died on table from arterial hemorrhage. Spleen, 400 gm., fibrotic and congested. Liver: a small piece removed at operation showed *toxic cirrhosis* microscopically. No autopsy.

CASE 25.—R. J., male, age 14. Ill 4 years in Cuba; following a febrile attack remained pale and weak. Chronic diarrhea, 6 to 14 daily stools, containing blood. Emaciated; spleen 10 cm. below ribs; liver not palpable. Blood, 26—2,261,000—4200; platelets moderately decreased. Splenectomy, death. Autopsy: ulcerative colitis involving entire colon and lower 40 cm. of ileum; spleen 780 gm., pulp greatly increased, great number of small, moderately distended sinuses, some fibrosis; liver 1200 gm., surface irregular and coarsely nodular, on section it presents very irregular islands of liver separated by connective tissue, microscopically it is typical *healed acute yellow atrophy.*

CASE 26.—E. S., female, age 16. For 5 months occasional edema and slight jaundice, urine constantly containing bile. Admitted with acute otitis media and later operated for mastoiditis, of which she died. Blood, 74—4,760,000—9100. Autopsy: spleen 620 gm., fibrotic; liver 670 gm., rough and nodular, microscopically *healed acute yellow atrophy.*

CASE 27.—M. D., alcoholic female, age 36. Epigastric distress after meals 15 years; hematemesis twice in 9 months; abdominal swelling 3 weeks. Neither liver nor spleen palpable because of ascites, which required frequent aspiration. Wassermann positive, but no improvement followed prolonged arsphenamin treatment. Blood, 40—2,240,000—4200; platelets slightly decreased. Splenectomy: liver greatly atrophied, its surface irregular, many adhesions; spleen high and adherent, 335 gm., fibrotic and congested, vessels sclerotic, Malpighian corpuscles not grossly visible. Blood, after operation and 3 transfusions, 81—4,650,000—6800; 4 months later, 75—3,910,000. Continued to require tapping about every 2 weeks, died of hematemesis 16 months after operation. Autopsy: peritoneum thickened, with massive adhesions everywhere; esophageal varices, probably site of recent hemorrhage; liver 1080 gm., capsule and portal connective tissue thickened so that islands of liver tissue are marked off, dense scars in places; single gall stone. Microscopically the liver shows large fibrous scars infiltrated with lymphocytes, no bile-duct proliferation. *Infectious cirrhosis,* presumably *syphilitic.*

CASE 28.—D. D., male, age 57. Syphilis at 17, Wassermann negative for past 4 years. Increasing pallor 3 years, recent dysuria and loss of weight. Yellowish pallor; liver 3½ cm. below ribs; spleen 6 cm. below umbilicus. Blood, 43—2,557,000—8200—normoblasts and megaloblasts—platelets normal—reticulocytes 4.2%; volume index 0.67; hemolysis in NaCl solutions begins at 0.525 and ends at 0.375%. Later leukocyte counts 3200 to 4300. Under radiation the spleen became smaller and general condition better. Refused splenectomy and died. No autopsy. Probably *syphilitic cirrhosis,* possibly hemolytic jaundice.

CASE 29.—S. G., syphilitic female, age 42. For 3 months pain in left upper abdomen and continuous flowing; lost 30 lbs. in 5 months. General condition poor; spleen 6 cm. below ribs, tender; liver not enlarged; ascites. Blood, 45—2,680,000—1850—Wassermann positive. Cancer of uterine cervix. Splenectomy: inoperable cancer of pelvis found at operation. Died, no autopsy. Spleen 1715 gm., fibrotic. Classed as *syphilitic cirrhosis.*

CASE 30.—J. P., alcoholic male, age 45. Nosebleeds for 6 months, dyspnea 10 months; jaundice 4 months ago. Marked emphysema; spleen 8 cm. below ribs; liver not enlarged; moderate ascites; edema of feet. Blood, 45—3,500,000—2800; platelets appear decreased; Wassermann positive. Before operation, 46—3,200,000—7600. Transfused, and splenectomy done; died. Autopsy: esophageal varices with minute rupture; melena; acute general peritonitis; S. hemolyticus in blood; aorta suggestive of syphilis; spleen 855 gm., fibrotic; liver 1380 gm., irregular (hepar lobatum) and other changes of *syphilitic cirrhosis;* splenic vein dilated to 1 cm.

CASE 31.—A. W., female, age 46. For 3 months bloody stools and pain in left abdomen. Spleen palpable. Blood, 48—3,000,000—4000; Wassermann positive. Under treatment with arsphenamin the blood improved and the spleen diminished in size. *Syphilitic cirrhosis.*

CASE 32.—G. C., female, age 65. At age 56 exploratory laparotomy was done, diagnosis splenic anemia, spleen not removed. Ill for 3 months, nausea, epigastric pain, hematemesis and swelling of abdomen and extremities. Spleen barely palpable; liver 7 cm. below ribs; ascites; slight jaundice; auricular fibrillation. Blood, 85—4,500,000—6250. Died of hematemesis. Autopsy: spleen large, showing microscopically congestion and fibrosis; liver small and cirrhotic, its appearance suggestive of toxic cirrhosis, but after examining microscopic sections the pathologist (F. B. Mallory), is unwilling to classify it; thrombosis of splenic and portal veins. *Unclassified cirrhosis.*

CASE 33.—R. F., alcoholic female, age 45. Abdominal distention 4 weeks. Spleen 6 cm. below ribs; moderate ascites. Blood, 84—4,900,000—4400, later 72—3,500,000. Died of hematemesis. Autopsy: spleen 1000 gm., fibrotic with marked distention of bloodvessels; liver 1380 gm., cirrhotic, marked cellular hyperplasia about vessels, some of which are completely obliterated; possibly syphilitic; portal and splenic veins sclerosed; ulcerative colitis. Classed as *atypical cirrhosis.*

CASE 34.—L. H., male, age 19. Pallor 1 year; abdomen swollen 1 week; diarrhea. Spleen 3 cm. below ribs; liver normal. Blood, 77—4,190,000—3550; platelets much decreased. Splenectomy: liver small and soft, with a "wavy" upper surface. Patient did not improve and died 2 months later of acute nephritis. Spleen fibrotic. *Cirrhosis of undetermined type.*

CASE 35.—A. K., female, age 25. Five months before admission vomited blood and a few days later aborted. Ascites tapped 3 times. Three months before admission operated for retroperitoneal abscess (right), followed by weekly tappings. Emaciated; marked ascites prevented palpation of abdominal organs. Blood, 36—4,110,000—7500; platelets decreased. Transfusion and splenectomy: many small mesenteric cysts; liver very small and hard, *type of cirrhosis not determined.* Required aspiration twice after operation; blood rose to 56—4,270,000—10,700. After 4 years patient is in excellent condition and ascites has not recurred. Spleen 420 gm., very marked fibrosis.

CASE 36.—M. A. L., female, age 45. At 34 had edema and ascites for 1 month, spleen and liver were large, heart markedly enlarged, with loud systolic murmur. Diagnosed splenic anemia. Blood, 45—2,726,000—3000; Wassermann negative. At 38 liver was palpable, spleen to umbilicus. Blood, 25—1,640,000—2400. Readmitted at 44; spleen 12 cm., liver 3 cm. below ribs; edge irregular and rough; marked ascites; blood, 19—1,390,000—1600. Refused splenectomy, died 5 months later. Autopsy: spleen 1350 gm., fibrotic, some phagocytosis; splenic vein patent; liver 1650 gm., *portal cirrhosis of undetermined type;* heart 400 gm., valves normal.

CASE 37.—I. N., female, age 53. Indefinite debility 10 years; diarrhea and abdominal cramps 6 weeks; mildly jaundiced at times. Spleen to umbilicus; liver 5 cm. below ribs. Blood, 39—3,480,000—2900; platelets reduced; hemolysis in NaCl solutions begins at 0.525, ends at 0.3%. Splenectomy: liver somewhat rough and appeared cirrhotic. Marked improvement in blood and general condition. Still well after 6 years. Spleen 705 gm., dilated sinuses and fibrosis. A bit of liver removed at operation showed slight *cirrhosis of undetermined type.*

CASE 38.—I. W., female, age 26. Double salpingectomy at 23, followed by persistent menorrhagia. Very pale; spleen 2 cm., later 5 cm., below ribs; liver not felt; no ascites. Blood, 18—2,190,000—3000. Several transfusions and splenectomy: liver small and scarred, possibly toxic cirrhosis.

Spleen fibrotic. Marked improvement. Menorrhagia continued for 2 years, when she was readmitted with blood 44—4,970,000—12,000. Transfusion and hysterectomy, followed by marked improvement in blood and general condition. *Cirrhosis of undetermined type.*

Case 39.—P. B., male, age 18. Admitted in an acute respiratory infection. Spleen 5 cm. below umbilicus; liver 6 cm. below ribs. No ascites. Blood, 60—3,542,000—4900; platelets normal. No operation. *Classed as non-cirrhotic liver disease.*

Case 40.—B. B., female, age 36. A sister and a niece have had splenectomies for causes unknown. Frequent gastric upsets with jaundice since a "grip" infection 4 years ago. No jaundice at present; liver slightly enlarged; spleen to umbilicus. Blood, 61—3,212,000—9500; icterus index 12; platelets normal; hemolysis in NaCl solutions normal; stool contains occult blood. Splenectomy: liver slightly enlarged. Spleen markedly fibrotic. After 9 months hemoglobin was 85 and patient's condition good. Classed as *non-cirrhotic liver disease.*

Case 41.—N. B., female, age 27. Appendectomy at 21, drained; operation followed by sepsis, relieved after a month by evacuation of an abscess "behind the liver." Operation at 25 for ventral hernia, dense adhesions found. Sixteen months later vomited blood and had tarry stools. Spleen 5 cm. below ribs, transversely located; liver not felt; no ascites. Blood, 75—3,500,000—3250; platelets appear decreased. Splenectomy and transfusion (750 cc.); liver very small, both it and spleen embedded in dense *adhesions.* Blood slowly improved to 80—4,000,000—11,630; platelets 256,000. General condition greatly improved. Spleen 680 gm., fibrotic, hemorrhages into trabeculæ, perisplenitis.

Case 42.—E. D., male, age 12. Appendectomy at 6; a year later severe hematemesis and ascites (aspirated); hematemesis again at 11. Spleen 4½ cm. below ribs; liver barely palpable. Blood 35—3,700,000—4000; fragility normal. Later leukocytes 4400 to 7150. Splenectomy: liver normal, dense *adhesions* about spleen, which was adherent to stomach. Spleen 525 gm., fibrotic, several small infarcts. Marked improvement; final blood 90—5,010,000—14,850.

Case 43.—M. H., female, age 40. Six operations since age 21, including appendicitis, gastric ulcer and ovarian cyst; repeated epistaxis for 18 months; several hemorrhages from stomach. Spleen easily felt; liver normal. Blood, 43—3,700,000—14,400; leukopenia never observed; hemolysis in NaCl solutions begins at 0.450, complete at 0.250%. Splenectomy: liver small, many firm *adhesions* about both liver and spleen interfered with satisfactory exploration. Died 2 days later; no autopsy. Spleen 250 gm., markedly fibrotic.

Case 44.—C. M., female, age 51. Appendectomy at 45, appendix gangrenous with a walled-off abscess and many adhesions. Emphysema; spleen 8 cm. below ribs; liver not felt; ascites. Blood, 32—3,360,000—5300, later leukocyte counts 2000 to 9800; Wassermann test positive. Readmitted at 59 with acute intestinal obstruction; operation and death from general peritonitis. Autopsy: gall bladder buried in old *adhesions,* which extend to surrounding viscera; spleen 880 gm., fibrotic; liver 1600 gm., microscopically normal; mesenteric vessels thrombosed, with infarction of gut.

Case 45.—H. D., not alcoholic, male, age 30. Appendectomy at 20; gastro-enterostomy at 26; hematemesis 6 months ago; pallor 5 years. Spleen 3½ cm. below ribs; liver normal; slight ascites. Blood, 26—2,478,000—3000; platelets decreased. *Adhesions.*

Case 46.—M. M., male, age 46. Known for years as a case of *congenital heart disease.* Recent hematemesis; loud systolic murmur and thrill; spleen to umbilicus; liver not felt; slight edema of feet and ascites. Blood, 53—3,590,000—4050, later 2600. Before operation, 70—3,750,000—4700;

platelets moderately decreased. Splenectomy: liver slightly enlarged, smooth and normal in consistency. Blood after operation, 98—5,000,000—10,650; platelets normal. Much improved and returned to laborious work. Spleen: blood sinuses well defined, walls thickened and consist of collagen reticulum in the meshes of which are numerous leukocytes and plasma cells; sinuses contain polymorphonuclears, lymphocytes and endothelial leukocytes, a number of which are phagocytic and contain lymphocytes and red corpuscles.

CASE 47.—R. C., female, age 30. Tumor in left abdomen 3 years. Its nature was not suspected till exploratory operation showed it to be a greatly *ptosed spleen*, which was removed. Blood, after operation, 75—5,680,000—13,800. Later, hemoglobin 95, leukocytes 10,600, eosinophils 25%. Spleen 470 gm., fibrotic, sinuses very distinct and dilated. Followed 20 months, during which time she remained well.

Summary. On the basis of a study of 47 cases the view is expressed that in the majority of patients presenting the clinical picture of Banti's disease (splenomegaly with fibrosis, microcytic anemia with leukopenia and a late stage with hemorrhages and ascites) the condition is dependent upon various intra-abdominal lesions obstructing the venous outflow of the spleen. By far the commonest of these is liver cirrhosis of various types. As Banti has limited the definition of the disease which bears his name in such a manner as to exclude these cases it is thought best to segregate them under a distinctive name. However, splenectomy is indicated just as in Banti's disease, regardless of the nature of the underlying lesion.

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THE DISTINCTION BETWEEN SPLENIC ANEMIA AND SUB-LEUKEMIC SPLENIC RETICULO-ENDOTHELIOSIS.*

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Not many decades ago, and within the memory of living physicians, cases of primary splenomegaly were classified as cases of leukemia, chronic malaria, or splenic anemia. Gradually, however, physicians have learned to recognize clinically as separate syndromes certain diseases simulating splenic anemia. The features characterizing these syndromes were clarified and simplified, and it became possible to diagnose clinically hemolytic icterus, syphilitic splenomegaly, chronic septic splenomegaly and, in a certain proportion of instances, Gaucher's disease, primary sarcoma of the spleen and subleukemic forms of leukemia. Now it is probable that it will be possible to divorce still another condition from the group of cases of splenic anemia and, if so, to save the patient the ill-advised ordeal of splenectomy. We refer to subleukemic splenic reticulo-endotheliosis, which at the time of examination is either an aleukemic or, more accurately, a subleukemic form of monocytic leukemia associated with splenomegaly as a prominent clinical feature.

The extent and importance of the reticulo-endothelial system is not generally appreciated; knowledge concerning its physiology and pathology is complicated and confusing. It is probable, however, that the studies of hematologists and tissue morphologists will lead the way to a clearer conception of clinical manifestations and their relation to pathologic findings. Special methods of cell staining and study, by trained observers, are necessary to the proper interpretation of both hematologic and pathologic data.

Active cells of the reticulo-endothelial system, both as histiocytes of the tissues and as syncytial cells of sinusoids, perform amazing functions in hemopoiesis, hemolysis, phagocytosis, storage of colloids and pigments, elaboration of substances to be passed on to other cells, metabolism of fats, lipoids, iron and hemoglobin, and in defense reactions of the body. Therefore, any clinical evidence of disorder of the reticulo-endothelial system must be regarded

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as an indication of profound organic and functional disturbance of the organism. The histiocyte of the reticulo-endothelial system is a partially differentiated cell and probably cannot, under normal conditions, act as parent cell of either lymphocyte or granulocyte. There is reason to believe, however, that under certain conditions the histiocyte may be the parent cell of the monocyte, although monocytes are usually derived from myeloblasts. Surely, if leukemic reticulo-endotheliosis and monocytic leukemia are not one and the same disease, they are closely akin.

In cases of leukemic reticulo-endotheliosis the primitive free reticulo-endothelial cell may be found in the blood in addition to the reticular type of monocyte. This primitive cell is generally larger than the leukocyte and usually has an eccentric nucleus, which is frequently elongated but may be rounded or indented. The nuclear membrane is clearcut, sharp and smooth, and one or two nucleoli may be present; the chromatin is blue with Wright's stain, sharply differentiated and arranged in fine granular strands. The cytoplasm is grayish-blue in contrast to that of the lymphocyte and blotchy or granular in appearance; cytoplasmic protrusions are common. The entire cell is youthful and delicate in appearance. Recognition of this cell in blood smears is a most important element in diagnosis.

Clinically, reticulo-endotheliosis may be manifest in three characters: (1) As storage or lipoid histiocytosis, of which Gaucher's disease, Niemann-Pick's disease and the Hand-Schüller-Christian syndrome are examples; (2) as infectious hyperplastic reticulosis, as in certain recurrent infections and sepsis, in infectious monocytosis, and in occasional cases of bacterial endocarditis; (3) as leukemic reticulo-endotheliosis.

Patients with leukemic reticulo-endotheliosis may present themselves with generalized involvement of the entire reticulo-endothelial system, with or without localized tumors, with predominant involvement of the bone marrow, predominant involvement of lymphatic structures, or predominant involvement of the liver or of the spleen. Any of these forms may be frankly leukemic (monocytic), subleukemic, or aleukemic. Leukemic splenic reticulosis is not difficult of recognition because of the high percentage of reticular monocytes in the blood; diagnosis of aleukemic forms may be clinically impossible. It is of the subleukemic type of splenic reticulo-endotheliosis that we wish to report 2 instances in which the diagnosis could have been made at an earlier date.

Case Abstracts. CASE 1.—A man, aged 33, had always been in good health until the present illness. During the preceding 5 years he had noticed some fatigability and slight loss of weight. During the preceding 3 years he had had 4 episodes like influenza associated with a vesicular eruption, chiefly of the wrists, elbows and knees. Splenomegaly had been noted only 2 weeks preceding examination, and weakness recently had

become more marked than before. The patient was only 5 feet 3 inches (160 cm.) tall, and weighed 106 pounds (48.1 kg.); his normal weight had been 115 pounds (52.1 kg.).

General physical examination, May 5, 1930, revealed nothing of apparent significance aside from very slight enlargement of the liver and considerable enlargement of the spleen. The spleen extended almost to the median line, and to the level of the umbilicus. The blood showed: hemoglobin, 12.7 gm. per 100 cc.; erythrocytes, 3,590,000 and leukocytes, 2600 per c.mm.; lymphocytes, 70.5%; monocytes, 1.5; neutrophils, 27; eosinophils, 0.5. (Subsequent study of blood smears led to the recognition of an occasional reticular cell.) One count of platelets, by the direct method, was 134,000 per c.mm., but platelets were very scarce in the smears. Bleeding time was 1.5 minutes and clot retraction was only slight at the end of 23 hours. The fragility test showed slight increase in resistance of erythrocytes. Urinalysis, serologic test of the blood, and roentgenologic examination of the thorax gave negative results. Liver function test showed no retention of dye; the value for serum bilirubin was 1.1 mg. per 100 cc. In spite of the delayed retractility of the clot and reduction in the number of platelets there had been no spontaneous hemorrhagic manifestations.

Splenic anemia was thought to be the most likely diagnosis, and splenectomy was performed May 28, 1930. The spleen was markedly enlarged, weighing 1050 gm.; there were few perisplenic adhesions. The liver seemed to be normal on palpation, and there was no enlargement of bloodvessels around the stomach.

The patient returned December 16, 1930. He was considerably better and had gained 9 pounds (4.1 kg.), but still felt exhausted. The blood showed 15.7 gm. of hemoglobin; 3,970,000 erythrocytes and 5200 leukocytes; lymphocytes, 61.5%; monocytes, 1.5; neutrophils, 36; eosinophils, 0.5; basophils, 0.5; reticulocytes, 0.5. Study of the smears disclosed definite macrocytosis, lymphocytosis and toxicated neutrophils; reticular cells were not recognized. Liver function test revealed no retention of dye; the value for serum bilirubin was 1.5 mg. per 100 cc.

The patient was next seen June 21, 1933, about 3 years following splenectomy. His condition had become very much worse during the preceding month, the complaints being chiefly of weakness, chilliness and anemia. His weight was not reduced; it was 110 pounds (49.9 kg.). He was pale and sallow, but not jaundiced. Superficial lymph nodes were not noticeably enlarged, although a few were barely palpable. The liver, however, had become definitely larger and extended three fingers' breadth below the costal arch. Liver function test, however, gave no evidence of retention of dye; the value for serum bilirubin was 1 mg. per 100 cc. There was some abdominal distention, slightly suggestive of retroperitoneal involvement. The blood showed: hemoglobin, 10 gm.; erythrocytes, 3,630,000; leukocytes, 8200; lymphocytes, 90.5%; monocytes, 2; neutrophils, 6.5; eosinophils, 1; reticulocytes, 0.3. Study of the smears disclosed no definite immaturity, aside from the presence of a few cells which were regarded as reticular in origin.

The patient was last under observation in December, 1933, 3½ years after splenectomy. December 9, 1933, the blood showed 7.6 gm. of hemoglobin; 1,520,000 erythrocytes and 6100 leukocytes; lymphocytes, 64.5%; neutrophils, 8.5; eosinophils, 1; reticulo-endothelial cells and reticular monocytes, 26. This high percentage of reticular cells led to a review of all former available blood smears, with the result that after prolonged study an occasional reticular cell could be found and reticular monocytes were not infrequently observed.

Treatment, which included transfusions and the use of Roentgen rays, effected no definite improvement and the patient was advised to return to

his home. When he last was heard from, in April, 1934, he was weak, anemic and in very poor health.

The spleen was examined by Dr. W. C. MacCarty, who reported: "The spleen weighs 1050 gm., is normally shaped and somewhat pale. Its density is slightly increased. The cut surface is smooth, red and fairly homogeneous in texture. Microscopically, the appearance of the organ simulates that of splenic anemia; however, there is in certain areas an increase in large ovoidal and spheroidal cells, apparently either of fibroblastic or reticuloblastic origin. The organ is congested and contains some intra-cellular and extra-cellular pigment. The Malpighian corpuscles are almost invisible, as are their germinal centers."

Dr. Hal Downey also examined sections. His report was as follows: "Microscopically, the spleen shows areas of hyperplasia of the reticulo-endothelium; there is not a uniform hyperplasia, however. Some small areas are very hyperplastic and seem to give rise to large, pale monocytoid cells. Much of the pulp seems to be fairly normal except for the occasional presence of these cells and the absence of lymphocytes. In a few places, reticular cells can be seen to form large plasmodia, which connect with the surrounding reticulum. A very few small follicles with germinal centers can be found. Lymphocytes are scarce. The splenic tissue indicates a diagnosis of leukemic reticulo-endotheliosis in the early stages" (Fig. 1).

Case 2.—A man, aged 50, for 10 months had had pain in the right leg, weakness and lassitude; and diagnoses of sciatica and neuritis had been made. In the course of the preceding 6 months a slight hemorrhagic tendency had developed, evidenced mostly by bleeding on shaving; there had been no gross hemorrhages. The patient had lost about 10 pounds (4.5 kg.); splenic enlargement had not been noted.

Physical examination, October 13, 1930, gave evidence of slight enlargement of the liver, and definite, although moderate, enlargement of the spleen. The blood showed: hemoglobin, 11.4 gm.; erythrocytes, 2,910,000; leukocytes, 2000; lymphocytes, 54%; monocytes, 2.5; neutrophils, 40; eosinophils, 3.5; reticulocytes, 0.9; platelets, 64,000 per c.mm. Bleeding time was 4.5 minutes; coagulation time of the venous blood, 10 minutes; calcium time, 9.5 minutes; prothrombin time, slightly prolonged, and retractility of clot was not present in 6 hours. Examination of blood smears gave no evidence of immaturity of cells; there was a slight tendency to macrocytosis, but no shift to the right of the polymorphonuclears. (Subsequent study of blood smears led to the recognition of 2% of reticular cells.) Serologic tests of the blood gave negative results. Roentgenologic examination of the right hip gave evidence of chronic destructive arthritis. A marked degree of prostatitis was demonstrated. On liver function test, no evidence of retention of dye was obtained.

After several days' consideration of the case the condition was, with some misgivings, classified as splenic anemia with secondary purpuric manifestations similar to those found in hemorrhagic purpura. Splenectomy was performed October 25, 1930. Adhesions about the spleen were few. There was no excess dilatation of veins, either in the splenic pedicle or around the stomach. The liver and gall bladder seemed to be normal.

Convalescence was satisfactory, and the patient was dismissed from hospital on the 14th day, at which time the value for hemoglobin was 57%; erythrocytes numbered 3,490,000; leukocytes, 4600 and platelets 440,000 per c.mm. of blood; clot retraction was satisfactory in 1 hour.

The patient returned for reëxamination 8 months later, July 27, 1931, stating that he had been very much improved until May, 1931, when he had begun to notice weakness and anemia. There had been no gross bleeding. The leukocyte count was said to have been very low, and at times the percentage of neutrophils was very low. The edge of the liver was

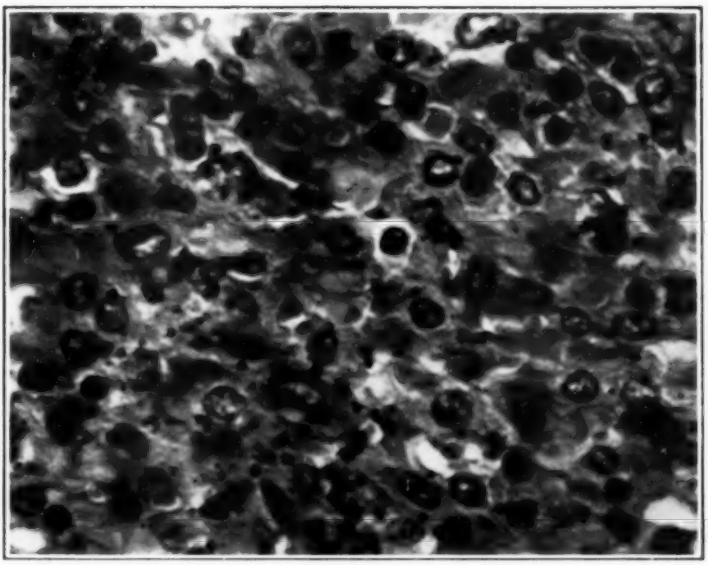

FIG. 1.—(Case 1.) Splenic tissue. Hyperplastic reticulum with reticular monocytes.

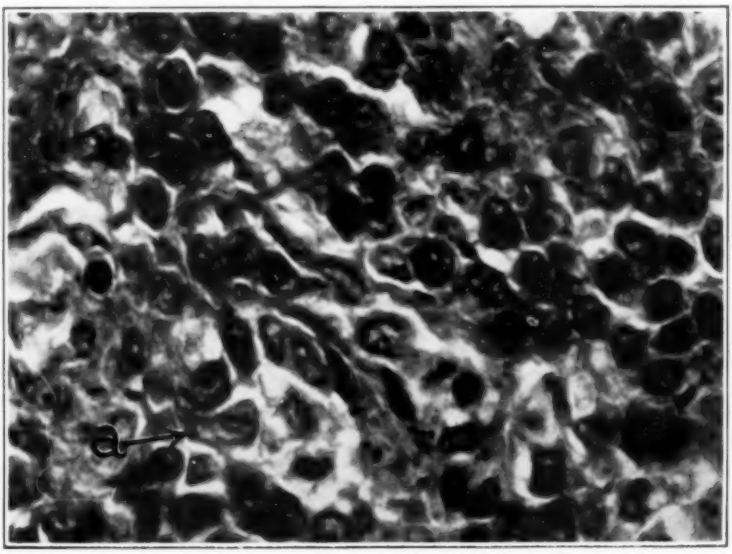

FIG. 2.—(Case 2.) Splenic tissue. Hyperplastic reticulum, with formation of reticular monocytes. *a*, Reticular cell in process of extrusion into splenic sinus.

just palpable; lymph nodes were not enlarged. Examination of the blood gave the following results: hemoglobin, 26%; 1,650,000 erythrocytes and 3600 leukocytes; lymphocytes, 50%; monocytes, 1; neutrophils, 28, and reticular cells and reticular monocytes, 21; occasional normoblasts were found; the percentage of reticulocytes was 0.4. Bleeding time was 3 minutes; coagulation time of venous blood, 5 minutes; calcium time, 10.5 minutes; prothrombin time, normal, and retractility of clot was not yet present in 7 hours. Platelet counts were 70,000 and 58,000 per c.mm. Roentgen films of the lower ends of the femurs and of the upper ends of the tibiæ were negative for evidence of abnormalities of bone.

Treatment was of no avail in combating the anemia and the patient was allowed to return home, where he died September 8, 1931. Necropsy was not obtained.

The spleen was examined by Dr. W. C. MacCarty, who reported: "The spleen weighs 800 gm. The density is slightly increased. The cut surface is homogeneous in texture. Microscopically, there is a generalized hyperplasia of large ovoidal and spheroidal cells, apparently of fibroblastic or reticuloblastic origin. Malpighian corpuscles are entirely obliterated. The tissues are congested and in places contain free red cells as well as pigment."

Dr. Hal Downey also examined the spleen, and his report is as follows: "This is one of the best specimens I have seen for evidence in favor of the derivation of monocytoid leukemic cells from reticulum. The structure of the spleen is very uniform, except that in some regions the number of free erythrocytes is greater than in others, and in certain areas free monocytoid cells are somewhat more numerous, while in other regions hyperplastic reticulum predominates. There is no nodular arrangement of leukemic cells and the follicles have disappeared.

"Monocytoid cells are large, rather pale, and contain relatively large, pale nuclei with one or two round nucleoli. Occasionally one sees a large or medium sized lymphocyte, but it is evident that the leukemic cells are not lymphocytes. The cytoplasm is very much less basophilic than that of lymphocytes and the nuclear pattern is different. The nuclei of the monocytoid cells are frequently indented and their cytoplasm is not as homogeneous and dense as that of lymphocytes. Normal sinuses are scarce. The connective tissue walls of the sinuses are usually thickened and some of the sinuses seem to have lost all of their syncytial cells. Two sinuses were observed in which the proliferating reticulum surrounding the sinus had broken through the wall. The nucleus of one of the reticulo-endothelial cells was within the sinus, that portion of the cytoplasm had become rounded, and a distinct pedicle extended from this rounded portion through an opening in the wall of the sinus to connect with the surrounding reticulum. Actual budding off of leukemic cells from hyperplastic reticulum can be seen in many places. In fact, the entire picture is typical of leukemic reticulo-endotheliosis of the type in which the leukemic cells of the blood are monocytoid in character and at the same time show evidence of their origin from cells of the reticulo-endothelial system" (Fig. 2).

Comment. The literature of leukemic reticulosis will not be reviewed at this time. Cases in which this condition has been recognized have been reported in increasing numbers within recent years; the total number in the literature is approximately 40. A few of these have conformed to the syndrome considered in this paper; namely, subleukemic splenic reticulosis.

Detailed and prolonged morphologic study of the blood is necessary to establish the diagnosis. Reticular cells and reticular mono-

cytes have been described early in this paper. Their recognition in blood smears is not difficult, but finding them in the early stages of the disease requires time. One is likely to classify them as mature monocytes, and their numbers may not be great enough to alter the normal percentage of monocytes. In the later stages of the disease the morphologic diagnosis is simpler because of the presence of a much higher percentage of reticular cells and reticular monocytes; in these cases they were, respectively, 26 and 21%. In both of the cases reported, reticular cells were not found on routine examination of the blood at the first visit, but on subsequent review of these blood smears reticular cells were demonstrated.

In the cases reported, macrocytosis of moderate degree, with hypochromasia, was present. The number of platelets was slightly reduced in Case 1 and markedly reduced in Case 2. The neutrophils showed a general shift to the left, their nuclei presenting some blurring of chromatin and irregularity of outline, and their cytoplasm containing granules which were larger than normal, were more basophilic, and were more irregularly placed. These toxic changes grew more marked as the disease progressed and the anemia became more severe.

The first patient presented a reduction of platelets and a delay of clot retraction; the second patient complained of free bleeding from cuts and had a low platelet count, a prolonged bleeding time and delayed retractility of clot. Hemorrhagic features have been noted also in reported cases. Leukopenia and an absence of leukocytosis were constant in these cases, even in the terminal stage of the disease; relative lymphocytosis also was present. Preceding episodes of infection were indicated by the histories. Liver function tests, even in the more advanced stages of the disease, revealed no retention of dye. It appears, therefore, that certain clinical features were present in these 2 cases which should have made one hesitate to diagnose splenic anemia and to search more carefully for reticulo-endothelial cells in the blood.

Summary and Conclusions. Two cases originally diagnosed as splenic anemia and subsequently classified as subleukemic splenic reticulo-endotheliosis are reported; the first of these was seen in an early stage of the disease; the second was more advanced at the time of the first examination. The clinical and morphologic features which should have suggested an earlier diagnosis of splenic reticulosis are as follows: history of preceding episodes of infection; a short history of the development of splenomegaly; slight purpuric manifestations with abnormalities of coagulation; leukopenia or normal leukocyte count with relative lymphocytosis and, in prolonged study of blood smears, the presence of reticulo-endothelial cells and the reticular type of monocyte. As the cases became more definitely leukemic, a higher percentage, between 20 and 30, of reticular cells could be found, even though leukocytosis was not present. The

advanced stages in both cases were characterized by severe macrocytic anemia, which did not respond to treatment. The infectious hyperplastic type of reticulo-endotheliosis, in which reticular cells may be found in the blood smears, can be distinguished from leukemic reticulo-endotheliosis by the presence of an increased percentage of polymorphonuclears, the absence of immature reticular monocytes, and clinical manifestations of a predominating infectious process. Cases of subleukemic monocytic myelosis reveal the presence of stem cells of the myeloid series and the absence of typical reticular cells.

In splenic anemia, there is usually no definite history of episodes of infection, a history of fever is uncommon and splenomegaly usually has been present for years. Purpuric features are occasionally present in cases of splenic anemia but apparently they are not nearly so common as with reticulo-endotheliosis. In splenic anemia the test of liver function almost always gives evidence of at least a moderate, and sometimes an extreme, grade of retention of dye, and gross gastro-intestinal hemorrhage is more common. Leukopenia with lymphocytosis is not uncommon in splenic anemia, but examination of blood smears, in addition to the absence of reticular cells, usually reveals more poikilocytosis and less macrocytosis. Prolonged study of blood smears is essential to the demonstration of the presence or absence of reticular cells, particularly in the early stages of splenic reticulosis.

COMPARATIVE VALUES OF SEVERAL ANTIDOTES IN CYANID POISONING.*

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Occupational cyanid poisoning may occur in the hydrocyanic acid fumigation of ships and buildings. For example, the United States Public Health Service, according to Surgeon General Cum-

* Read in part before the American Public Health Association at Indianapolis, October 10, 1933; the Indianapolis Medical Society, February 13, 1934; and the American Society for Pharmacology and Experimental Therapeutics at New York, March 29, 1934.[1] Preliminary reports were also made to the Society for Experimental Biology and Medicine.[2,3]

ming, annually fumigates from 2000 to 3000 vessels in its quarantine work. Potassium cyanid or hydrocyanic acid is frequently used in photography, electroplating, metallurgy, and gilding, and must therefore be considered a potential danger to the lives of those who are engaged in such professions, unless adequate precaution is exercised.

Accidental deaths have resulted from eating nuts or other parts of plants that produce cyanophoric glucosids, such as bitter almonds. There are in the vegetable kingdom at least 360 varieties in 148 species and 41 families yielding hydrocyanic acid.

An arrow grass of the species *Triglochin maritima* has been fatal to livestock in Western States, due to its content of hydrocyanic acid. According to Beath, Draize and Eppson,[4] the small shoots of regrowth collected at the end of September may assay as high as 77 mg. of hydrocyanic acid per 100 gm. of the green plant.

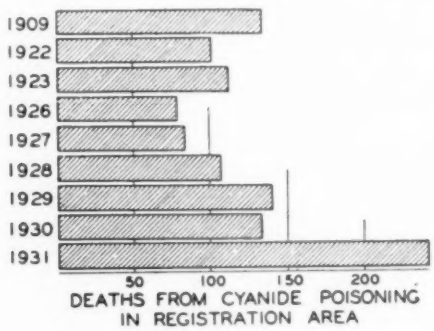

FIG. 1.

From 1909 to 1931 (Fig. 1) there have been 79 to 243 deaths annually from cyanid poisoning in the registration area of the United States. On the average, therefore, the mortality rate is about 1 to 2 per 1,000,000 population. In large cities, the death rate may be relatively higher. For example, in San Francisco, with a population of 634,394 in 1930, there were 8 deaths from cyanid poisoning in 1928, 10 in 1929, 11 in 1930, 12 in 1931, and 21 in 1932.[5]

The highest incidence of deaths from cyanid poisoning are due to suicide. Thus, in 1931 of the 243 deaths due to cyanid poisoning in the United States, 241 were suicidal. All the San Francisco deaths from 1928 to 1932 were also the result of self-murder.

Status of Previously Proposed Antidotes. A comprehensive review of the earlier literature on hydrocyanic acid and its derivatives and antidotes has been made by Hunt.[6] It suffices here to mention the various chemical agents that have been advocated for the treatment of cyanid poisoning. One class of antidotes contains sulphur; of these sodium thiosulphate is the best known. The results of

Lang,[7] Heymans and Masoin,[8] Meurice,[9] Hunt[10] and Hug[11] indicate that sodium thiosulphate has to a certain degree some detoxifying effect in animals poisoned with a cyanid, particularly if it is introduced into the circulation beforehand. In spite of the limited efficacy of the thiosulphate therapy, favorable clinical reports have been made by Lassaga,[12] Feyerabend[13] and Buzzo.[14,15] In 2 cases of cyanid poisoning, sodium thiosulphate was injected intracardially.[16,17]

Another sulphur-containing compound, sodium tetrathionate, was shown by Hebting,[18] Chistoni and Foresti[19] and Draize[20] to have an antidotal action against cyanid poisoning.

Evidence of antagonism between other sulphur-containing substances, such as sodium sulphid, cystin, cystein, thio-acetic acid, β-thiolactic acid, α- and β-dithiodilactylic acids, thioglycolic acid, glutathion, sodium seleniosulphate, and colloidal sulphur, on the one hand, and cyanid on the other, was furnished by Lang,[7] Hebting,[18] Voegtlin, Johnson, and Dyer,[21] Meurice,[22] Milanesi[23] and Forst,[24] but from a practical point of view there is no indication that they are better than sodium thiosulphate.[25,26]

Dihydroxyacetone injected prior to the poison affords protection in animals as reported by Forst,[24] Rentz,[27] and Turner and Hulpieu.[28] Similarly, glucose or glucose with insulin, administered beforehand, has been shown to exert an antagonistic action against cyanid by Violle[29] and others.[30,31,32,24] On the contrary, Voegtlin, Johnson, and Dyer,[21] Heymans and Soenen,[33] Hynd,[34] and Turner and Hulpieu[28] failed to notice any prophylactic value of glucose. A large number of other carbohydrates have been tested in cyanid poisoning by Forst,[35] but the majority of them are useless if poisoning has already taken place.

Although cobalt nitrate appears to have some protective value in animals against cyanid poisoning,[36,7,9] it is itself a relatively toxic substance. Potassium permanganate and hydrogen peroxid might be expected to be efficient chemical antidotes of cyanid, but the results of Walko[37] and Muntsch[38] indicate nothing of practical importance. Certain depressants, such as scopolamin and morphin, may postpone the onset of convulsions, but they do not seem to reduce the toxicity of cyanid.[39,27]

Circumstances Leading to Present Investigation. In 1932 Geiger[40] reported a case of cyanid poisoning successfully treated with methylene blue and, later, 2 other cases which recovered. The adoption of methylene blue therapy was based upon the work of Sahlin,[41] Eddy,[42] Brooks,[43] Hug[11] and Hanzlik.[44] Hug[45] and Wendel,[46] working independently, came to the conclusion that the antidotal action of methylene blue is due to the formation of methemoglobin which, in turn, reacts with the cyanid ion to form a much less toxic compound, cyanmethemoglobin.

Our primary interest in the problem was to ascertain quantita-

tively how many fatal doses of cyanid can be detoxified by methylene blue. In one paper, we showed that by the injection of the dye, animals were saved from 2 fatal doses.[47] Amyl nitrite given by inhalation, on the other hand, antidotes 4 fatal doses.

After the appearance of our paper,[47] it was our good fortune to learn by personal communication that an American physician, Doctor Pedigo,[48] in 1888 proved beyond doubt the value of amyl nitrite against cyanid poisoning in dogs. Unfortunately, his article has not been listed in easily available indices or mentioned in textbooks, so that it is difficult for later investigators to be aware of his important work. The delay in appreciating his results has probably also caused the tardy development of the nitrite therapy.

Another paper that deserves special mention is that of Mladoveanu and Gheorghiu[49] who in 1929 demonstrated the unquestionable benefit of sodium nitrite in both anesthetized and unanesthetized dogs during cyanid intoxication. Evidence was presented that this nitrite saved animals from several fatal doses of potassium cyanid.

Work was continued in our laboratory on other nitrites and sodium thiosulphate and tetrathionate. In view of the fact that none of the substances detoxified more than 4 lethal doses of cyanid, it was finally decided to try combination therapy, especially because a synergistic action was noted by Forst[24] with dihydroxyacetone and colloidal sulphur, and by Turner and Hulpieu[28] with dihydroxyacetone and sodium thiosulphate. Meanwhile, Hug[50] and Buzzo and Carratala[51] made studies along the same line with reference particularly to the combination of sodium nitrite and sodium thiosulphate, and their reports have promptly appeared. In general, there is mutual confirmation of their results and ours.

Experimental Procedure. All the experiments were made on a group of 193 dogs weighing from 7 to 24.6 kg. (average 14.2), 186 of which were unanesthetized. In the early stages of the investigation, mice and rabbits were also employed, but they were found to be less suitable because of their relatively more rapid death from cyanid poisoning. In them, the various antidotes in order to be effective should be given preferably some time before the poison. In the dog, on the other hand, more precise results may be obtained and better comparisons can be made with different detoxifying agents. Furthermore, if a substance has a high antidotal action, it is almost always possible to demonstrate in dogs its efficacy during the late stages of cyanid poisoning; for example, immediately after respiratory failure.

The compounds studied in cyanid poisoning included methylene blue, nitroglycerin, amyl nitrite, sodium nitrite, sodium thiosulphate, sodium tetrathionate, combinations of sodium thiosulphate with sodium nitrite or amyl nitrite, and sodium tetrathionate with sodium nitrite or methylene blue. All of the substances, as well as sodium cyanid, were of the highest purity, conforming with U. S. P. requirements. The first lot of sodium tetrathionate, which is not official in the U. S. P., was courteously supplied by Dr. O. A. Beath, the Agricultural Experimental Station, University of Wyoming, to whom we are greatly indebted. The remaining amount of

sodium tetrathionate was prepared by ourselves, at Dr. Beath's suggestion, according to Biltz and Biltz (transl. by Hall and Blanchard).[52]

In each unanesthetized dog, the antidotal agent was given slowly by vein at the same time the sodium cyanid gained entrance into the body (subcutaneously). In several cases the poison was administered first and promptly followed by the antidote. The recorded antidotal value can therefore be termed maximal for each substance or combination since it was estimated under the most favorable conditions. No prophylactic action was determined, that is, by giving the antidote beforehand, because it had no bearing on the practical therapy. Solutions of 4 to 10% of sodium cyanid were employed depending upon the size of the dose to be administered. The dog was observed continuously day and night, and its pulse and respiratory rates were counted at frequent intervals. When signs of poisoning, such as vomiting, convulsions, and respiratory or circulatory embarrassment, persisted for longer than the first hour or reappeared in

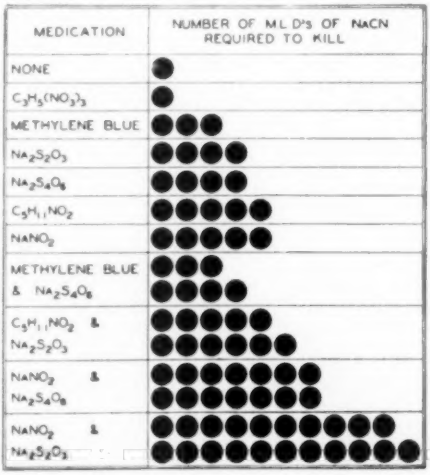

FIG. 2.—Comparison of antidotal action of different substances in dogs.

the course of experimentation, the antidote was repeated in usually one-half of the initial dose. No animal was pronounced recovered until it was free from all signs of poisoning, accepted its food, and resumed its ordinary activity. Amyl nitrite was the only substance that was administered by inhalation, the technique of which was previously described.[47] A criterion of 3 out of 5 dogs was adopted in the majority of the cases to determine the highest dose of cyanid an antidote would detoxify.

Experiments were also carried out with sodium amytal, washed red blood corpuscles, insulin, glucose, and adrenalin, in the treatment of cyanid poisoning.

Results. Our data are summarized in Table 1 and illustrated in Figure 2. The minimal lethal dose (M.L.D.) of sodium cyanid in dogs by subcutaneous injection was determined to be 6 mg. per kg. of body weight. The results with antidotal medication may be discussed in Table 1, p. 772.

1. *Nitroglycerin.* This substance is not a true nitrite, although it has an action similar to that of a nitrite. In the present studies, 2 to 5% solutions in propylene glycol were employed. Dogs receiving 10 to 20 mg. per kg. all had violent convulsions but recovered. A dose of 5 mg. per kg. was not

TABLE 1.—COMPARISON OF ANTIDOTAL ACTION OF VARIOUS SUBSTANCES IN CYANID POISONING IN DOGS.

NaCN.		Antidotal medication.	Number of dogs used.	Number of dogs recovered.	Highest No. of M.L.D.'s of NaCN detoxified.
Mg. per kg.	M.L.D.				
5	0·8	None	3	2	0
6	1		10	2	
6	1	Methylene blue	2	2	2
12	2		4	3	
18	3		3	0	
12	2	Sodium thiosulphate	3	3	3
18	3		5	3	
24	4		3	0	
12	2	Sodium tetrathionate	5	3	3
18	3		3	3	
24	4		3	0	
18	3	Amyl nitrite	2	2	4
24	4		5	3	
30	5		6	0	
24	4	Sodium nitrite	5	3	4
30	5		5	2	
36	6	Methylene blue and sodium tetrathionate	1	1	6(?)
42	7		1	0	
48	8		1	0	
54	9		1	0	
60	10	Amyl nitrite and sodium thiosulphate	5	3	10
66	11		3	0	
72	12		3	0	
78	13		3	0	
72	12	Sodium nitrite and sodium tetrathionate	5	3	13
78	13		4	3	
84	14		5	2	
60	10	Sodium nitrite and sodium thiosulphate	4	3	20
72	12		4	3	
78	13		5	3	
120	20		7	4	
126	21		3	0	

able to detoxify 2 M.L.D.'s of sodium cyanid in animals—one dog died in 21 hours and 50 min., and the other in 38 min. There was little indication that nitroglycerin had an antidotal action.

2. *Methylene Blue.* A 1% solution of the dye, freshly prepared, was injected 1 to 5 min. after the cyanid. It should be noted from Table 1 that methylene blue in the dosage of 200 to 550 mg. per kg. can detoxify only 2 M.L.D.'s of sodium cyanid. Trautman[53] found that in rabbits methylene blue was useless in hydrocyanic acid gas poisoning. Furthermore, Sahlin[41] emphasized the toxicity of methylene blue, and Macht and Harden[54] recently reported wide variations of toxicity in commercial samples of the dye, even though they were all labelled U. S. P. quality.

3. *Sodium Thiosulphate.* A 50% solution of this well-known substance, freshly made, was injected by vein. It was surprising that such a hypertonic solution, when carefully injected, did not cause any sloughing or local edema. The compound has a very low toxicity, for dogs receiving 3 gm. per kg. showed no signs other than vomiting during the first hour. In the dosage of 1 or 2 gm. per kg., sodium thiosulphate saved dogs from 3 M.L.D.'s of sodium cyanid.

4. *Sodium Tetrathionate.* This sulphur compound is less stable in aqueous solution (25%) than sodium thiosulphate, although it has the same antidotal value in a dosage of 500 mg. per kg. Sodium tetrathionate caused vomiting in dogs when doses of from 0.5 to 0.75 gm. per kg. were injected intravenously. A dose of 1.0 gm. per kg. killed; hence it is more toxic than sodium thiosulphate.

5. *Amyl Nitrite.* By repeated inhalations, dogs were saved from 4 M.L.D.'s of sodium cyanid as already described in a previous paper.[47] Some animals required as many as 102 inhalations.

6. *Sodium Nitrite.* Each morning a 4% aqueous solution was freshly prepared for the experiments of the day. The M.L.D. of sodium nitrite in dogs by rapid injection was found to be 45 mg. per kg. In cyanid poisoning one-half of the M.L.D. of the nitrite, that is, 22.5 mg. per kg., was given in the first dose, but it was reduced to 10 mg. per kg. in subsequent doses. Several dogs surviving the cyanid poisoning received total amounts of 72.5 to 92.5 mg. of sodium nitrite per kg. The efficacy of sodium nitrite is equal to that of amyl nitrite; that is, it antidotes 4 M.L.D.'s of sodium cyanid in the majority of cases.

7. *Methylene Blue and Sodium Tetrathionate.* In 5 dogs poisoned with sodium cyanid, methylene blue (200 mg. per kg.) was injected and immediately followed by sodium tetrathionate (500 mg. per kg.). Although the number of experiments was too small, yet the results seem to indicate that this combination at its best saves dogs from 6 M.L.D.'s of sodium cyanid. An additional animal was given 8 M.L.D.'s of the cyanid and treated with methylene blue and sodium thiosulphate, with no success.

8. *Amyl Nitrite and Sodium Thiosulphate.* Intravenous injection of sodium thiosulphate and repeated inhalations of amyl nitrite detoxified in dogs 10 M.L.D.'s of sodium cyanid, beyond which the combination became ineffective.

9. *Sodium Nitrite and Sodium Tetrathionate.* Dogs injected intravenously with sodium nitrite and then sodium tetrathionate, survived 13 M.L.D.'s of sodium cyanid. The initial dose consisted of 22.5 mg. of sodium nitrite per kg., and sodium tetrathionate, 500 mg. per kg., the subsequent doses being 10 and 250 mg., respectively. Recovery occurred even when the treatment was instituted after respiratory failure.

10. *Sodium Nitrite and Sodium Thiosulphate.* The best antidotal action was observed with successive injections of sodium nitrite and sodium thiosulphate (Fig. 2). It was found that the optimal initial dose of sodium nitrite was 22.5 mg. per kg., and that of sodium thiosulphate, 1.0 gm. per

kg. Subsequent doses of the nitrite should be 10 mg. per kg., and those of the thiosulphate, 0.5 gm. per kg. As shown in Table 1, 4 out of 7 dogs were saved from 20 M.L.D.'s of sodium cyanid by such medication. Death was delayed for several hours in those animals which did not survive. The efficacy of the nitrite-thiosulphate combination diminishes if the initial doses are either increased or decreased. For example, by injecting an initial dose of 22.5 mg. of sodium nitrite and 2.0 gm. of sodium thiosulphate, per kg. of body weight, only 13 M.L.D.'s of sodium cyanid were detoxified, as stated in our preliminary report.[2]

The action of sodium nitrite is prompt. It abolishes or decreases convulsions and often puts the poisoned dogs on their feet within a few minutes. Sodium thiosulphate, on the other hand, is comparatively slow in its effect, and does not appear to inhibit convulsive movements like the nitrite. One feature that was observed and should be pointed out is the conversion of a rapidly fatal course of cyanid poisoning to prolonged remissions with occasional reappearance of toxic signs. There was a period of stupor or depression following the use of the antidotes. The 4 dogs receiving 20 M.L.D.'s of sodium cyanid required from 42 to 47 hours for complete recovery under the nitrite-thiosulphate treatment. The nitrite and the thiosulphate should be repeated when there is an occurrence of vomiting, hyperexcitability, tremor, dyspnea, or tachycardia. Sometimes it is a wise measure to administer them prophylactically even in the absence of the signs. However, under no circumstances should they be repeated oftener than once per hour. As the experiment progresses the frequency must be greatly reduced, say, once every 3, 4, or 8 hours. Rapid accumulation of sodium nitrite is just as serious as cyanid poisoning for it increases the degree of asphyxia. Two of our surviving animals received total amounts of 122.5 mg. of sodium nitrite per kg., and 6 gm. of sodium thiosulphate per kg. in 11 doses.

The beneficial effect of the nitrite-thiosulphate therapy is convincingly demonstrated in Figure 3. The dog on the left hand side received 1 M.L.D. of cyanid. It vomited repeatedly 9 min. after the injection of the poison, went into convulsions in 21 min., and died in 53 min. The dog on the right hand side had 10 M.L.D.'s of cyanid. Following the poison sodium nitrite and sodium thiosulphate were injected in order. The dog vomited once 23 min. after the introduction of the poison, but it was able to stand up on its feet practically all the time. To insure complete detoxification of the cyanid, the nitrite and the thiosulphate were repeated in 1 hour 50 min., and 3 hours 50 min. The dog appeared perfectly normal in 20 hours 35 min. The experiment could not be duplicated with methylene blue, sodium nitrite alone, or sodium thiosulphate alone.

The antidotal action can be illustrated in another manner. In Figure 4, the respiratory movements of an anesthetized dog are graphically recorded. At the beginning of the experiment a volume

of 4 cc. of the cyanid (M/50) was injected by vein in the course of 1 min. This was followed by the familiar respiratory stimulation which, according to Heymans, Bouckaert and Dautrebande,[55] is due chiefly to carotid sinus reflexes. Upon the return of the respiration to the initial rate and amplitude, a 1% solution of sodium nitrite was injected intravenously at the rate of 4 cc. per min. until a dose of 22.5 mg. per kg. had been reached. The injection was then continued with a 50% solution of sodium thiosulphate at the same rate until a quantity of 1 gm. per kg. had been administered. The resumption of sodium cyanid at the rate of 4 cc. per min. after

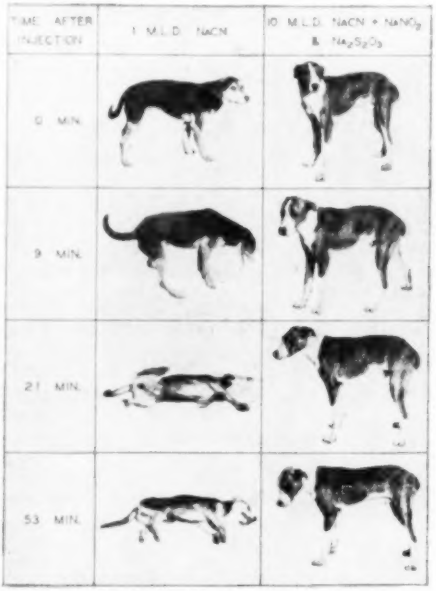

FIG. 3.—Contrast of treated and untreated animals. Dog on the left-hand side, male, weighed 13.7 kg. and received subcutaneously 6 mg. of sodium cyanid per kg. of body weight. Dog on the right-hand side, male, weighed 14.8 kg. He was given 60 mg. of sodium cyanid per kg. Simultaneously with the poison, sodium nitrite in the dosage of 22.5 mg. per kg. was injected intravenously, and followed by 2 gm. of sodium thiosulphate per kg. See text for further details.

the thiosulphate now produced no respiratory stimulation. When more than 2 M.L.D.'s of sodium cyanid had been given (the M.L.D. in anesthetized dogs by intravenous injection is approximately 3 cc. of M/50 solution per kg.), the amplitude of the respiration became gradually larger. The dog stopped breathing after 8 M.L.D.'s of the cyanid had been introduced. The same experiment was made with 6 other anesthetized dogs, and the results were confirmatory of those just described. The total amount of the cyanid required to kill those animals varied from about 6 to 9 M.L.D.'s.

To give a crucial test of the nitrite-thiosulphate therapy, a few dogs were injected with large doses of sodium cyanid, and allowed to develop dangerous signs of poisoning, such as convulsions, loss of corneal reflex, and in 1 case cessation of respiration, although the heart was still beating. It was found that, by the intravenous injection of the nitrite and the thiosulphate after the appearance of these dangerous signs, several dogs were revived from 10, 13, and 15 M.L.D.'s of the cyanid. It did not seem possible to save dogs that had been poisoned for some time with 20 M.L.D.'s of cyanid. This is to be expected because the efficacy of an antidote diminishes as poisoning becomes well advanced.

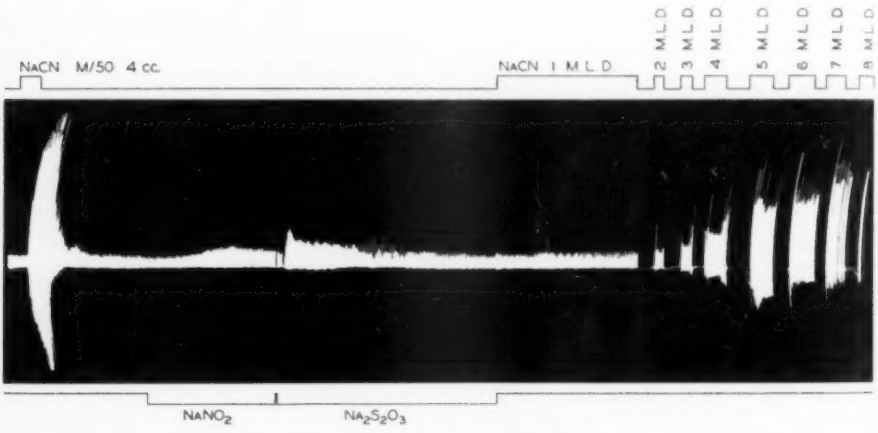

FIG. 4.—Detoxification of cyanid as shown on respiration. Dog, female, weighing 9.3 kg., was anesthetized with phenobarbital sodium subcutaneously, 0.15 gm. per kg. The tracing of respiration should be read from left to right. After the first M.L.D. of sodium cyanid had been injected, the drum was stopped. At the end of the second M.L.D., it was started again for a short distance, and so on until the animal died. See text for explanation.

Hug[50] reported that dogs receiving 6 M.L.D.'s of hydrocyanic acid were saved with sodium nitrite and sodium thiosulphate. He further stated that if hydrocyanic acid was injected by vein at the rate of 0.2 mg. per kg. per minute, dogs died with a dose of 0.8 mg. per kg.; but if sodium nitrite and sodium thiosulphate were administered, more than 8 mg. of the poison per kg. were detoxified. Buzzo and Carratala[51] claimed that in rabbits sodium nitrite and sodium thiosulphate injected intravenously antidoted 18 M.L.D.'s of potassium cyanid which was given by mouth. This work needs confirmation, particularly because of the fact that according to these authors[14] sodium thiosulphate alone overcame 10 M.L.D.'s of cyanid—a figure twice as great as that observed by Lang[7] under the same conditions. In our own laboratory, no rabbits treated with the nitrite and the thiosulphate survived more than 6 M.L.D.'s of cyanid which was injected subcutaneously.

11. *Miscellaneous.* Two dogs poisoned with 5 M.L.D.'s of sodium cyanid, but treated with amyl nitrite, were injected intravenously with washed red blood corpuscles, prepared from another dog, with the hope that the added amount of hemoglobin would increase the capacity of detoxification. Although the transfusions prolonged the surviving period, they did not alter the outcome of the experiments, that is, the animals finally died. Hematuria promptly appeared. An anesthetic dose of sodium amytal with no other medication was injected by vein into another dog receiving 2 M.L.D.'s of cyanid. Convulsions did not occur but respiration failed in 22 min. The suppression of convulsions alone contributed no benefit to the course of cyanid poisoning. There was another dog that had 5 M.L.D.'s of sodium cyanid and received, in addition to amyl nitrite inhalations, insulin and glucose. It died in 1 hour 6 min. There was no evidence that glucose and insulin had any favorable influence upon cyanid poisoning. During the terminal stages of two additional experiments, adrenalin was given intravenously, but it failed to delay the fatal outcome. Obviously, stimulation of the circulation did not postpone the respiratory failure.

Discussion. Of the list of substances that have an antidotal action in cyanid poisoning (Table 1), methylene blue has the least efficacy. Sodium thiosulphate and sodium tetrathionate are equal in value. Amyl nitrite and sodium nitrite are both twice as effective as methylene blue. The most interesting feature is the synergism and potentiation of action of the nitrites on the one hand and the sulphur compounds on the other. The combination of sodium nitrite and sodium thiosulphate detoxified 20 M.L.D.'s of sodium cyanid, which is almost 3 times the sum of their individual values, and fully 10 times as effective as methylene blue alone. A slight potentiation of action also appears to exist between methylene blue and sodium tetrathionate.

No attempt was made to determine the mechanism of cyanid detoxification in this investigation, but there has been a sufficient accumulation of published data to warrant a tentative explanation. It is well known that nitrite ions react with hemoglobin. Hug[45,56] and Wendel[46] recently pointed out that the formation of cyanmethemoglobin by cyanid ions and methemoglobin accounted for the detoxification of the cyanid. Previously, Rosenthal and Voegtlin[57] had already observed an antagonism between methemoglobin and cyanid on the rat testis (Warburg's apparatus). The pigment cyanmethemoglobin was first prepared by Kobert[58] and crystallized by Zeynek.[59] According to Barnard[60] cyanid combines with the iron of the methemoglobin molecule. Cyanmethemoglobin must be many times less toxic than cyanid.

Another mode of detoxification, the conversion of cyanid to sulphocyanate, has been suggested by numerous workers. Sulphocyanate is a relatively harmless radical. It is normally found in salivary secretions.

In the combined action of sodium nitrite and sodium thiosulphate, then, the following three reactions probably take place:

$$NaNO_2 + \text{Hemoglobin} \rightarrow \text{Methemoglobin} \quad [I]$$

$$NaCN + \text{Methemoglobin} \rightleftarrows \text{Cyanmethemoglobin} \quad [II]$$

$$Na_2S_2O_3 + NaCN + O \rightarrow NaSCN + Na_2SO_4 \quad [III]$$

When the nitrite is injected alone, the sulphur is furnished by the thio-constituents of the body, such as cystein, glutathion, etc. It is not improbable that the chief function of the nitrite is to pick out the cyanid from various tissues and convert it to cyanmethemoglobin *via* methemoglobin. The real detoxification of the cyanid is its conversion to sulphocyanate, which is mainly brought about by the sodium thiosulphate administered, and to a less extent by the cystein and glutathion of the body. Recently Lang[61] demonstrated that the formation of sulphocyanate in the organism was catalyzed by an enzyme to which he gave the name rhodanase. When sodium nitrite and sodium thiosulphate are used together, it seems that the speed of conversion from cyanid to sulphocyanate is much accelerated. This results in the potentiation of the antidotal action of these two substances. On the other hand, equation [II] may be reversible so that in course of time free cyanid ions are liberated and typical poisoning signs reappear. Meanwhile, part of the sodium thiosulphate may have been eliminated. This explains the necessity for repeating the antidotes during the course of an experiment.

The above explanation does not exclude other methods of cyanid detoxification, but as far as the evidence goes the formation of cyanmethemoglobin and sulphocyanate probably plays the most important rôle.

A question arises as to why all the nitrites, as well as methylene blue, do not have the same degree of potentiation of action since each compound forms methemoglobin with hemoglobin. It must be recognized, however, that the similarity of this group of substances is only qualitative. The effect of amyl nitrite is quick but brief, and that of sodium nitrite slower but more prolonged. The convulsant action of nitroglycerin is synergistic with that of cyanid. According to Hug[56], a dose of 40 mg. of sodium nitrite per kg. converts 56 to 83% of hemoglobin to methemoglobin. Methylene blue, on the other hand, has a lower capacity of forming methemoglobin[62]—so much so that it was not possible to demonstrate the presence of methemoglobin in the blood of poisoned cases.[40] Amyl nitrite alone has the same antidotal action as sodium nitrite, but in association with sodium thiosulphate it does not potentiate as much as the latter. Buzzo and Carratala[63] obtained similar results in rabbits. The question of methemoglobin concentration may also be concerned with the difference of action here.

The favorable results of the nitrite-thiosulphate therapy in dogs against cyanid poisoning warrant trials in human cases, especially because both sodium nitrite and sodium thiosulphate are well known in medicine. Mota[64] has already saved a case of cyanid poisoning with sodium nitrite, the total amount injected being 0.57 gm. The temporary depressor action apparently caused no damage. As pointed out above, sodium thiosulphate has also been employed for the same purpose. While the most suitable dosage of the combination remains to be established, we would suggest

using 6 to 10 mg. of sodium nitrite per kg., and 0.5 gm. of sodium thiosulphate per kg. For an adult of 50 kg., therefore, the first dose would consist of 0.3 to 0.5 gm. of sodium nitrite and 25 gm. of sodium thiosulphate. Subsequent doses should be one-half of that quantity. The two substances must not be mixed for administration.

It may be reiterated here that the prognosis of any case of cyanid poisoning depends upon the dose of the poison taken and the promptness of treatment—the earlier the better. Assuming that the quantity of cyanid absorbed is not too great, a rational treatment, based on animal experiments, would be: (*A*) immediate administration (inhalation) of amyl nitrite by an assistant for from 15 to 30 sec., to be repeated every 2 to 3 min. until the physician has filled his syringes with the antidotal solutions; (*B*) intravenous injection of sodium nitrite at the rate of 2.5 to 5 cc. per minute, followed by sodium thiosulphate at the same rate, care being taken to avoid extravasation; (*C*) gastric lavage if the poison is taken by mouth—preferably done by another physician for division of labor; (*D*) continuous observation of the patient for at least the first 24 to 48 hours. A temporary improvement of the patient's condition after initial medication does not insure ultimate recovery or indicate discontinuance of watching. When signs of poisoning persist or reappear 1 hour after the initial dose, the nitrite and the thiosulphate may be repeated. If there is no indication for repeating the antidotes, a second injection may be given 2 hours after the first for prophylactic purposes.

A kit for the treatment of cyanid poisoning should be prepared and installed in ambulances and emergency units of large hospitals. This should consist of:

12 Pearls of amyl nitrite
2 Ampules of sodium nitrite, 0.3 gm. in 10 cc. of water
2 Ampules of sodium thiosulphate, 25 gm. in 50 cc. of water
1 Sterile syringe, 10 cc. size, with a 22-gauge needle
1 Sterile syringe, 50 cc. size, with an 18-gauge needle
1 File
1 Stomach tube

During recent years, studies have been made to find substitutes for hydrocyanic acid for the fumigation of ships.[65,66] If, however, hydrocyanic acid continues to be used for fumigation, some efficacious antidote, such as the kit proposed above, should be provided either on the ship or conveniently located at the dock. It may be reminded that the fatal course of poisoning by hydrocyanic acid gas is shorter than that by its salts, potassium or sodium cyanid, so that therapeutical measures must be instituted immediately.

In agriculture, the veterinarian may try out the same dose of sodium nitrite and sodium thiosulphate as proposed for men for sheep poisoned with arrow grass. In horses and cattle, multiples of the same should be employed.

Summary. An antidotal action against cyanid poisoning is possessed by methylene blue, sodium thiosulphate, sodium tetrathionate, amyl nitrite, and sodium nitrite.

A potentiation of antidotal action occurs when a nitrite or methylene blue on the one hand, and sodium thiosulphate or sodium tetrathionate on the other, are successively administered.

The highest antidotal action is exhibited by the combination of sodium nitrite and sodium thiosulphate. Under the most favorable conditions in dogs, this combination detoxifies 20 minimal lethal doses of sodium cyanid, and is 10 times as effective as methylene blue. Recovery has occurred even when the two substances are given at the late stages of cyanid poisoning.

A technique for employing sodium nitrite and sodium thiosulphate in clinical trials has been suggested.

We wish to express our thanks to Messrs. Robert C. Anderson, Davis Rawlings, Robert Fink, Hans Schulze, Leo J. Freihage, John Hansen, William Winchester and Herschell Griffin for their assistance in numerous experiments.

ADDENDUM. While this manuscript was going to press there appeared two papers, one by Viana, Cagnoli and Cendan[67] and the other by Hanzlik and Richardson.[68] The former article was on 2 cases of cyanid poisoning successfully treated with the same antidotes we are proposing. The first case was that of a young girl who took 5 gm. of potassium cyanid. She received 1 ampule of amyl nitrite and a total amount of 1.5 gm. of sodium nitrite and 18 gm. of sodium thiosulphate. Although she developed severe cyanosis, recovery occurred. The second patient, a woman, ingested 2 gm. of potassium cyanid. She was administered 1 ampule of amyl nitrite and a total quantity of 0.75 gm. of sodium nitrite and 12 gm. of sodium thiosulphate. She also survived. In the report of Hanzlik and Richardson, they presented data on sodium nitrite and sodium thiosulphate, confirmatory of our results, but they argued that methylene blue should be considered the antidote of first choice in cyanid poisoning.

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ON THE INHERITANCE OF DIABETES MELLITUS.

III. THE BLOOD SUGAR VALUES OF THE RELATIVES OF DIABETICS.

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THE analysis of the genetic basis of diabetes susceptibility indicates that a number of apparently normal relatives of diabetics are in fact potential diabetics.[1,2] The identification of these persons, destined because of their genetic constitution to develop the disease, is of some consequence from both a practical and a theoretical point of view. We have accordingly determined the blood sugar concentrations of 169 close relatives of known diabetics, on the assumption that abnormal concentrations might yield a clue to the presumable potential diabetics among them. In order to determine the limits of normal blood sugar concentrations we also examined a group of 125 control individuals.

Two sets of examinations were employed: (1) A set of routine venous blood sugar determinations, ordinarily taken 2 or more hours after a meal, and (2) a set of glucose and sucrose tolerance tests. These two groups of examinations will each be presented separately and then the relation of our findings to the Mendelian basis of the disease will be discussed.

Routine Blood Sugar Determinations. In Fig. 1 we present graphically the various blood sugar concentrations determined for 76 controls and an equal number of relatives of diabetics; also the statistical constants of these data. The control individuals are a group of non-diabetic patients *none of whom* had any immediate family history of diabetes. It will be noted that the mean blood sugar concentration in this group is 94.2 mg. per 100 cc. compared with a mean value of 101.3 for all the relatives of diabetics. A χ^2 comparison of the data of Fig. 1 gives a value of $P = 0.01$. This indicates a significant difference between the distribution of blood sugar values in the two groups. It is obvious from inspection of Fig. 1 that this difference is largely due to the presence of a number of abnormally high blood sugar concentrations in the experimental series.* Eleven (14.5%) of the values in the experimental

* Not only are the frequency distributions significantly different in our two series, but also the variance, *e. g.*, the ratio $\frac{\sigma_1^2}{\sigma_2^2}$ is 5.25. For $P = 0.01$ this ratio is 3.29 (see Snedecor[3]) and P is, therefore, much less than 0.01 in this series.

series lie at 140 or beyond in Fig. 1. If the experimental series represented a normal group of persons exactly comparable to our control series we should expect 0.37% of the determinations to lie at 140 or beyond. We can designate as a "limiting hyperglycemic value" 138.2 mg. per 100 cc. of blood, since blood sugar concentrations higher than that would occur once in 200 trials.*

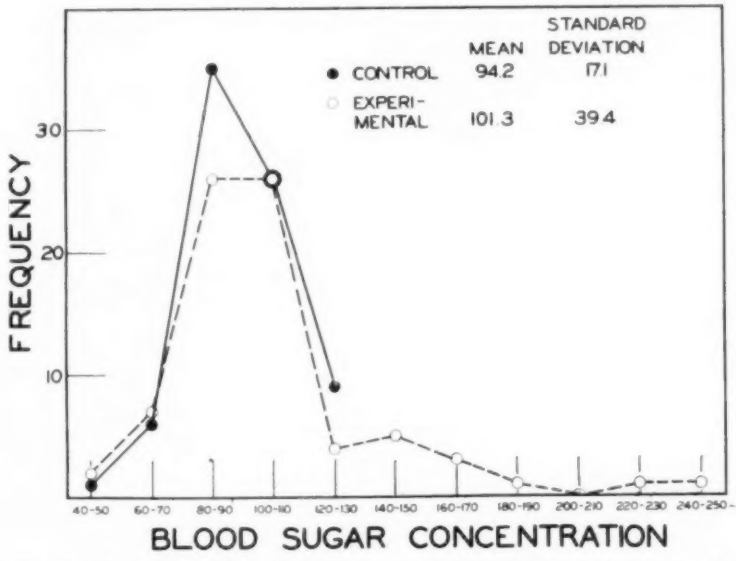

FIG. 1.—Frequency distributions for blood sugar concentrations in routine blood sugar determinations taken upon a control series and upon a series of relatives of diabetics. Blood sugars are given in mg. per 100 cc. of blood.

It may be objected that high blood sugar concentrations are encountered in non-diabetic persons of advanced age, and that the exceptional cases in our series represent elderly persons. This is not the case. The median age of the 11 exceptional persons is 34 years, and 9 of them are below 40 years of age. In fact, the population from which our standard control values are derived is a much more elderly group than our experimental series; the median age of the control series is about 50 years, that of the experimental series 26 years, so that our control data are definitely biased against the experimental data if the age factor is important. Actually, our control series does give a slight indication that the routine blood sugar values are slightly higher in older persons: of the 36 persons less than 50 years of age, 24 (66.66%) had blood sugar concentrations of less than 100 mg. per 100 cc., and of the 40 persons

* A value of 15 or above would occur less than once in 1000 trials, and a value of 16 or above once in 10,000 trials, yet we observe 9 of the former and 7 of the latter in these 76 observations.

above the age of 50, only 18 (45%) had blood sugar concentrations below 100 mg. per 100 cc. The difference is significant statistically (difference = 21.66%—probably error of difference = 5.3%, $\frac{\text{difference}}{\text{PE}_D} = 4.07$).

Sugar Tolerance. The 49 individuals employed as controls for the sugar tolerance series were normal healthy persons with no diabetic histories. Their median age was closer to that of the 95 relatives of diabetics given similar tests; the median ages in the two groups were 28 and 31 years, respectively.

Both glucose and sucrose tolerance tests were given: 100 gm. of glucose or 75 gm. of sucrose were taken 2 or more hours after a meal. No significant difference was found in the blood sugar values in the two tests. A definitely significant difference was observed between capillary and venous bloods, however, and accordingly the control series was divided into two groups: (1) 21 individuals whose capillary blood sugar concentrations were measured, and (2) 28 individuals whose venous bloods were taken. The capillary bloods were taken chiefly from very young and very old persons.

TABLE 1.—MEAN BLOOD SUGAR CONCENTRATIONS IN A SERIES OF CONTROL SUGAR TOLERANCE TESTS.

Hours after sugar ingestion.	Blood sugar concentration (mg. per 100 cc.).		Standard deviation (± mg. per 100 cc.).	
	Venous.	Capillary.	Venous.	Capillary.
0	74	98	84	139
½	103	146	248	201
1	85	126	275	180
2	75	102	155	182

The statistical constants of the data for the various determinations in the control series are given in Table 1 and in Fig. 2. Again, if we set as the limiting hyperglycemic value a blood sugar concentration equal to the mean value plus $2.5768 \times \sigma$, we observed at once that in our experimental series there are a number of high blood sugar concentrations (Table 5). These are summarized in Table 2.

TABLE 2.—THE NUMBER OF "SUPERNORMAL" BLOOD SUGAR VALUES AT VARIOUS TIMES DURING THE SUGAR TOLERANCE TESTS OF DIABETIC RELATIVES.

Time	Total No. of determinations.	No. of "supernormal" values.	"Supernormal," per cent.
0	62	5	8.1
½	95	11	11.6
1	94	7	7.4
2	91	10	11.0
Totals	342	34	9.9

Actually the 34 "supernormal" values were obtained from 24 individuals, some of whom gave abnormally high values more

than once. These 24 individuals represent 25.3% of the 95 tested. In our control series of 49 persons a "supernormal" value was encountered only once (at the 2d hour) and then in a postoperative patient. The sugar tolerance tests revealed more "supernormal" persons than the routine blood sugar determinations. An inspection of Table 2, however, reveals that the percentage of "hyperglycemic" values was about the same at 0 hours as at ½, 1 and 2 hours. This we believe to be deceptive, since the highest values were encountered after sugar ingestion (see Table 5). If we discount the 0 hour determinations, 19 individuals (20%) showed "supernormal" blood sugar concentrations after sugar ingestion.

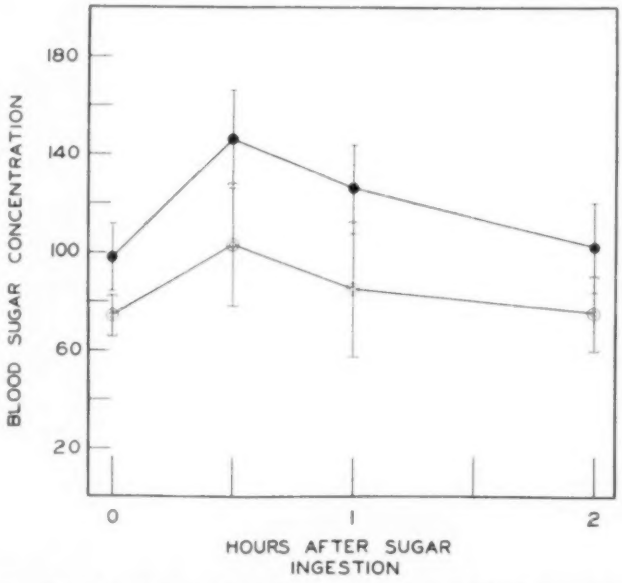

FIG. 2.—Mean blood sugar values (in mg. per 100 cc. of blood) for venous (open circles) and capillary (closed circles) bloods in control groups of normal, healthy persons. The vertical lines above and below the mean values are equal to the standard deviations of these values (Tables 1 and 4).

The Results of Blood Sugar Determinations in Various Types of Matings. Our assumption that diabetes will develop in persons homozygous for a recessive gene (*e. g.*, *mm* individuals) requires that *all* the offspring of 2 diabetic parents should one day develop diabetes (since the matings are *mm* × *mm*). We have, therefore, taken special pains to collect information on the families of as many conjugal diabetics as possible and have found 33 such families with a recorded total of 138 offspring. Of the children in these families, 20 have had either tolerance tests or routine blood sugar examinations. Of these 20, 5 gave hyperglycemic values, but 15

gave normal blood sugar values (see Table 3). If our Mendelian assumptions are correct this means that neither routine blood sugar determinations nor tolerance tests will give a clue to *all* the potential diabetics; nor would we expect such tests to reveal all potential diabetics, since it is well known that persons with completely normal tolerance curves may, at varying times after the test is given, develop diabetes. It is interesting to inquire, however, to what extent the discovery of hyperglycemia may be taken to indicate genetically diabetic individuals.

We arrange the classifiable matings as follows: (1) Neither parent diabetic; (2) one parent diabetic; (3) both parents diabetic. Matings (3) must on our Mendelian hypothesis be $mm \times mm$. Matings (1) and (2) may be taken provisionally as $Mm \times Mm$ and $Mm \times mm$, respectively, since they produced at least 1 diabetic child; but it must be kept in mind that a few of the parents in each group who are non-diabetic may be mm, since they have not developed diabetes though destined to do so. In Table 3 (see Table 6 for the age incidence relations) we summarize the diabetes incidence among the children in these various groups of matings, the extent of hyperglycemia and the expectation of diabetics on the basis of the life tables for potential diabetics presented in our previous paper.[2] (Tables 1 and 2.) The expectations for the $mm \times mm$ matings are immediately applicable to the observations, since we have no way of estimating the missing mm parents in the other two groups of matings.* As in our previous analysis, Joslin's incidence data call for a relatively high incidence compared to the more generalized incidence data based on Massachusetts incidence. The observations in the $mm \times mm$ matings do not depart significantly from either set of expectations, though again they agree more closely with the expectations based on Massachusetts incidence.

But the most interesting relation established by the data of Table 3 is the proportion of hyperglycemic individuals in the three types of matings. In the matings designated $Mm \times Mm$ (carrier $\times$ carrier), 6.8% of the tested non-diabetic offspring were hyperglycemic, in $Mm \times mm$ (carrier $\times$ diabetic), 17.9%, and in $mm \times mm$ (diabetic $\times$ diabetic), 25%. These percentages are in the ratio 1:2.6:3.7. Now the simple Mendelian probabilities for such matings are in the ratio 1:2:4 (*e. g.*, $\frac{1}{4}:\frac{1}{2}:1$), and the ratios of presumed unidentified mm individuals are 1:2.2:3.9 on the basis of Joslin's onset data and 1:2.1:4.7 on the basis of the Massachusetts tables. If the "hyperglycemic" blood sugar examinations indicate merely the random distribution of peculiar individuals, then we should expect the percentages of "hyperglycemics" in the various matings to be in the ratio 1:1:1. Actually the number of

* In our previous analysis,[1,2] we were able to do this, since the families were successive families appearing for treatment. The families in this series were selected for examination, particularly the $mm \times mm$ group.

TABLE 3.—THE INCIDENCE OF DIABETES AND HYPERGLYCEMIA AMONG THE CHILDREN IN VARIOUS TYPES OF MATINGS AND THE EXPECTATION OF DIABETES ON THE ASSUMPTION THAT DIABETES DEVELOPS AS A RECESSIVE CONDITION.

TABLE 3.—THE INCIDENCE OF DIABETES AND HYPERGLYCEMIA AMONG THE CHILDREN IN VARIOUS TYPES OF MATINGS AND THE EXPECTATION OF DIABETES ON THE ASSUMPTION THAT DIABETES DEVELOPS AS A RECESSIVE CONDITION.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Type of mating.	Total No. children.	No. of diabetic children.	No. of "hyperglycemic" children revealed by exam.	No. of children tested for "hyperglycemia."	Per cent "hyperglycemic."	Diabetic children expected (Joslin data).	Diabetic children expected (Mass. data).	Diabetic siblings observed.	Diabetic siblings expected (Joslin).	Diabetic siblings expected (Mass.).
Neither parent diabetic ($Mm \times Mm$)	126	49	3	44	6.8	45.38	44.12	6	2.38	1.12
One parent diabetic ($Mm \times mm$)	95	27	7	39	17.9	23.19	22.06	7	3.19	2.06
Both parents diabetic ($mm \times mm$)	138	30	5	20	25.0	41.49	22.40	—	—*	—*

* These expectations are not calculated, since the families were selected because both parents were diabetic. The expectations of columns (7) and (8) should be compared directly with the observed number in column (3).

TABLE 6.—SUMMARY OF THE INCIDENCE OF DIABETES AND HYPERGLYCEMIA IN VARIOUS MATINGS.

Decade.	Neither parent diabetic.					One parent diabetic.					Both parents diabetic.			
	Diabetic patients.	Diabetic siblings.	Non-diabetic siblings.	Hyperglycemic siblings.	Siblings tested for hyperglycemia.	Diabetic patients.	Diabetic siblings.	Non-diabetic siblings.	Hyperglycemic siblings.	Siblings tested for hyperglycemia.	Diabetic children.	Non-diabetic children.	Hyperglycemic children.	No. of children tested.
1 . . .	31	1	34	1	17	6	1	10	2	6	1	24	—	1
2 . . .	9	1	30	2	24	5	1	11	3	10	3	6	—	3
3 . . .	1	2	6	..	3	2	—	22	—	15	—	15	1	6
4 . . .	—	—	1	..	..	4	2	8	1	5	2	29	4	9
5 . . .	—	1	—	..	..	1	1	4	1	1	10	11	..	1
6 . . .	1	—	1	..	..	1	2	4	..	2	9	6		
7 . . .	1	—	1	..	..	1	..	2	..	..	4	8		
8 . . .	..	1	1	..	..	..	..	..	..	..	1	3		
Totals .	43	6	74	3	44	20	7	61	7	39	30	103	5	20

observations is too small to give any exact significance to these ratios;* but the result is suggestive, indicating that these hyperglycemic individuals *may* be potential diabetics (*e. g., mm* individuals). A larger series would undoubtedly resolve this possibility.

If we assume that these hyperglycemic individuals do represent

TABLE 4.—SUMMARY OF BLOOD SUGAR CONCENTRATIONS IN TOLERANCE TESTS ON A CONTROL POPULATION.

Blood sugar (mg. per 100 cc.)	Hours after sugar ingestion.							
	0	0	½	½	1	1	2	2
	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.
40 to 50	...	...	...	...	1	...	2	
60 to 70	15	2	4	...	12	...	17	1
80 to 90	12	3	8	...	8	...	4	7
100 to 110	...	13	7	...	3	7	3	7
120 to 130	...	1	6	7	2	8	1	5
140 to 150	...	...	3	9	2	5		
160 to 170	...	...	...	3	...	1		
180 to 190	...	...	...	2				
Totals	27	19	28	21	28	21	27	20

TABLE 5.—SUMMARY OF BLOOD SUGAR CONCENTRATIONS IN TOLERANCE TESTS ON RELATIVES OF DIABETICS.

Blood sugar (mg. per 100 cc.).	Hours after sugar ingestion.							
	0	0	½.	½	1	1	2	2
	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.
40 to 50	1	...	...	...	...	...	2	
60 to 70	11	...	3	...	11	...	31	
80 to 90	41	...	8	...	25	1	26	2
100 to 110	7	1	24	...	17	—	16	1
120 to 130	1	...	23	2	16	2	7	1
140 to 150	...	...	17	2	10	1	—	1
160 to 170	...	...	7	4	4	4	1	1
180 to 190	...	...	2	—	—	...	—	
200 to 210	...	...	2	1	1	...	—	
220 to 230	...	...	...	...	1	...	—	1
240+	...	...	...	...	1†	...	1‡	
Totals	61	1	86	9	86	8	84	7

* A value of $P < 0.05$ is obtained on a χ^2 test for independence. This indicates a probably significant difference between the three groups.

† 320 mg. per 100 cc.

‡ 350 mg. per 100 cc.

future diabetics, then we can determine roughly the extent of prediction of diabetes that these tests afford. Taking the *mm* × *mm* cross alone, 25% of the children examined were hyperglycemic; then presumably a similar percentage would be revealed among the children we did not examine. We would expect to find 25 additional hyperglycemic individuals, or a total of 30 among 108 individuals listed as non-diabetic. If, for the moment, we assume that these 30 individuals are "diabetic," then there is revealed a total of 60 diabetics among the 138 offspring, or about 45% in a group of potential diabetics whose median age in 35 years. On the Massachusetts incidence data this is the percentage we would expect to identify as diabetic in a completed population (subject to 1920 death rates) with a median age of about 53 years (and on Joslin's data at a median age of about 48 years). Thus our blood sugar examinations may be taken to have enabled us to foretell by many years the future diabetics. We can make no exact calculations of the extent of this anticipation, since we would have to employ the hazardous procedure of determining the distribution of age at onset of diabetes in a population destined to live beyond age 90, and, furthermore, we would have to make other assumptions about the random occurrence of hyperglycemia which cannot be made until the relation of hyperglycemia to the age of tested individuals is established.

Discussion. Obvious obstacles prevent the collecting of the rather large set of data that would permit a completely satisfactory statistical resolution of the significance of the presence of hyperglycemic individuals in diabetic families. None the less it is clear that an excessive number of high blood sugar values do occur in such families when comparison is made with a carefully collected control series. We would like to stress here that the blood sugar values that we have termed hyperglycemic are *not* necessarily diabetic blood sugar values; they are abnormal on the basis of our control series. To establish the limits of diabetic blood sugars we should have a series of exact determinations of blood sugar values among persons with uncontrolled diabetes; this we do not have, and, on *a priori* grounds, it seems highly doubtful that such a series could be satisfactorily assembled. But our investigation does indicate that the establishment of a set of "normal" blood sugar values require the strict exclusion of near relatives of diabetics. Therefore, any calculation of "normal" values based upon data not so guarded is open to criticism if it is used to set a limit to normality. Even when careful inquiry reveals no family history of diabetes there always exists the possibility that undetected potential diabetes is present in certain families. More delicate tests for latent diabetes would, of course, obviate much of the purely formal difficulties here presented. It is hoped that such tests may be available.

Summary. Approximately 14% of a group of relatives of diabetics given routine blood sugar examinations and 25% of those given sugar tolerance tests had abnormally high blood sugar values when comparison is made with similar determinations made upon control groups of normal healthy persons with no family history of diabetes incidence. When we examine, in various types of matings, the incidence of such "hyperglycemic" persons among the offspring, the data suggest that such individuals may be taken as future diabetics, since the ratios of them in these matings are approximately proportional to the ratios of presumed unidentified genetically diabetic individuals called for by the Mendelian hypothesis advanced to explain the inheritance of diabetes. These tests do not, however, reveal all the genetically diabetic individuals. It is pointed out that if these tests have any general significance, they indicate that the establishment of normal blood sugar values requires the strict exclusion of relatives of diabetics from the group of normal persons supplying the data.

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CARBOHYDRATE METABOLISM IN HUMAN HYPOTHYROIDISM INDUCED BY TOTAL THYROIDECTOMY.*

I. THE GLUCOSE TOLERANCE CURVE AND THE FASTING SERUM SUGAR CONCENTRATION.

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Investigations concerning the effect of hypothyroidism on carbohydrate metabolism in man have given rise to varying opinions. The fasting blood sugar in non-diabetic patients with hypothyroid-

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ism has been found normal[3,4,5] or low.[4,6] After glucose administration in non-diabetic patients with hypothyroidism, some authors have found a normal response;[1] others have found a subnormal rise in blood sugar;[2,3] while still others have concluded that the blood sugar rises higher and returns to the fasting level more slowly than in normal individuals.[4,5,6]

Because of this disagreement, we have availed ourselves of an opportunity to study the effect of hypothyroidism on carbohydrate metabolism under controlled conditions: we have measured the fasting serum sugar concentration, the blood sugar tolerance curve following ingested glucose, and the blood sugar changes following insulin injection in a group of non-diabetic patients before and after the development of the hypothyroid state, induced by total thyroidectomy[7] performed for its therapeutic effect on chronic heart disease.[8] In addition, these studies have been made on one patient who had diabetes and on one who, before operation, had mild hyperthyroidism as well as heart disease. In this note studies on the fasting serum sugar concentration and on the blood sugar curve following the ingestion of 100 gm. of glucose are reported. The second report of this series[9] deals with the blood sugar changes following the subcutaneous administration of insulin before and after total thyroidectomy.

Methods of Investigation. Venous blood samples were utilized in the glucose tolerance studies. In 4 of 13 cases in which serum sugar measurements were made, arterial blood was utilized; in the remaining cases venous blood was employed. The serum and whole blood sugar measurements were made by the method of Folin and Wu,[10] 5% sodium tungstate and ⅔ normal sulphuric acid were used to precipitate the serum proteins. Urine sugar was estimated by the qualitative Benedict method. The basal metabolic rates were made in duplicate with a Collins-Benedict-Roth apparatus and calculated according to the Aub-Dubois normal standards.[11] Basal metabolic rate measurements were made on the same day or within a few days of the time when the blood was drawn for sugar analysis. The sugar tolerance test meal consisted of 100 gm. of glucose mixed with the juice of a lemon and dissolved in water up to 500 cc. Blood samples were collected before and one-half, one, two and three hours after ingestion of the glucose solution. Urine specimens were collected at each of these intervals if the patient was able to void.

The patients studied were operated on for the relief of long-standing congestive heart failure or of angina pectoris. The preoperative tests were made a few days before operation when the patients with congestive heart failure were edema-free and in condition suitable for operation; these patients were all edema-free and able to be up and about at the time of the postoperative tests. None of the patients with angina pectoris had suffered from an attack of anginal pain on the morning of the test. The diets of these patients were adequate in carbohydrate.

When tests were made one month or longer after operation clinical evidences of hyperthyroidism were manifest and the basal metabolic rates were usually between −20 and −30%. Some of the patients were receiving small doses of thyroid to prevent the development of untoward symptoms of myxedema, in accord with considerations outlined elsewhere.[12]

Results. *Fasting Serum Sugar Concentration.* Studies of the serum sugar before and at intervals up to 1 year after total thyroidectomy were made in 13 patients who showed no evidences of diabetes or thyrotoxicosis before operation (Table 1). Since a mild anemia develops in hypothyroidism, serum rather than whole blood was utilized for these studies, thus obliterating the effect of change in red cell volume on the sugar concentration. In 9 of the 13 cases the fasting serum sugar concentration decreased somewhat when hypothyroidism developed; at the sixth postoperative month the average decrease in these 9 cases was 12 mg. per 100 cc.; in 2 cases the serum sugar concentration did not change, and in the remaining 2 cases increased slightly (Table 1). Measurements in 3 patients (Cases 2, 3, and 4) (Table 1) as early as 2 weeks after operation revealed a slight decrease both in the fasting serum sugar and in the basal metabolic rate. All postoperative serum sugar concentrations were within the accepted normal limits.

TABLE 1.—FASTING SERUM SUGAR CONCENTRATIONS IN HUMAN HYPOTHYROIDISM FOLLOWING TOTAL ABLATION OF THE NORMAL THYROID GLAND.

			Serum sugar concentration—mg. per 100 cc.				
Case	Age.	Preop. diagnosis.*	Before operation.	2 wks.–1 mo. postop.	6 mos. postop.	9 mos. postop.	1 yr. postop.
1. (E. W.)	27	C. H. F.	91	75	73		
2. (W. B.)	55	C. H. F.	93	87	79	...	89
3. (C. C.)	66	C. H. F.	90	71	75		
4. (A. B.)	57	A. P.	88	85	74		
5. (L. B.)	44	C. H. F.	96	..	84	87	82
6. (F. C.)	31	C. H. F.	68	..	92	83	77
7. (L. M.)	53	C. H. F.	107	..	99		
8. (W. D.)	22	C. H. F.	79	..	80	95	91
9. (B. Z.)	45	C. H. F.	94	..	84	101	100
10. (M. F.)	48	A. P.	92	..	92		
11. (E. P.)	58	A. P.	98	..	90		
12. (M. W.)	54	A. P.	91	..	117		
13. (M. C.)	57	A. P.	129	..	118		
Average B. M. R. % deviation from normal† . . .			−5	−17	−30	−27	−26

* C. H. F. refers to congestive heart failure; A. P. to angina pectoris.

† Two patients (Nos. 3, 11) were given small doses of thyroid (Armour's) from the end of the first postoperative month, 6 other patients (Nos. 4, 5, 6, 8, 10, 13) received small doses of thyroid beginning with the 3d to 6th postoperative months.

Glucose Tolerance. Glucose tolerance tests were made before total thyroidectomy in 8 patients who showed no clinical evidence of diabetes or hyperthyroidism, and in the same patients at intervals after operation when conclusive clinical and laboratory evidences of hypothyroidism were present (Table 2). Thirteen glucose tolerance tests were made in 8 other patients only after total thyroidectomy (Table 3). In many of our cases the height and duration of the hyperglycemia following the ingestion of 100 gm. of glucose before operation were greater (Table 2; Fig. 1) than usually obtained in young normal individuals.[13,14] Since our patients had heart dis-

ease and since many were above middle age (Table 2), this high normal type of glucose curve might be expected.[14]

TABLE 2.—AVERAGE RESULTS IN CASES IN WHICH TESTS WERE MADE AT POSTOPERATIVE INTERVALS ONLY.

No. of cases.	Age range.	Time of study.	B. M. R., % deviation from normal.	Serum sugar values following 100 gm. of glucose by mouth, mg. per 100 cc.					Urine sugar, gm.	Thyroid medication.
				Fasting.	Time after glucose.					
					30 min.	60 min.	120 min.	180 min.		
7	22–66	2–3 mos. postop.	−27	79	124	138	125	96	0	No thyroid in 6 cases; gr. ½ daily in 1 case.
4	22–66	4–6 mos. postop.	−29	79	136	148	134	111	0	Thyroid, gr. ½ to ¾ daily in 2 cases.
2	22–66	10–13 mos. postop.	−27	88	135	121	107	92	0	Thyroid, gr. ½ daily in 1 case.

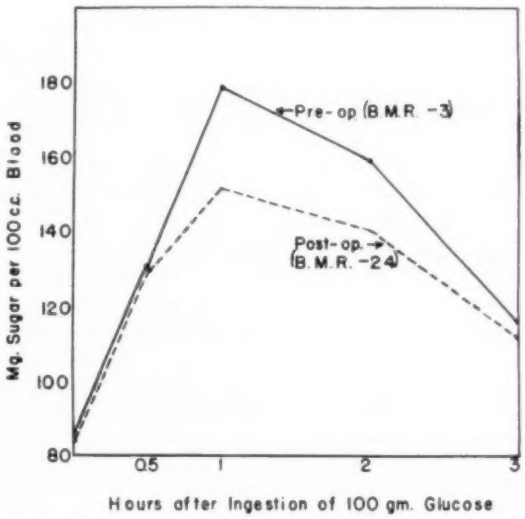

FIG. 1.—Average glucose tolerance curves before and after total thyroidectomy in a group of 7 patients, none of whom had evidence of diabetes or thyrotoxicosis prior to operation.

The glucose tolerance curves following total thyroidectomy were not strikingly different from those obtained before operation in the same subjects (Table 2); the only significant change in response to the glucose meal which may be attributable to the induced hypothyroidism was the somewhat low sugar concentration 1 and 2 hours after glucose, evident in 6 of 7 cases (Table 2; Fig. 1). In

Case 9 (Table 2) glucose (40 cc. of 50% solution) was administered intravenously; in this patient the maximum increments in blood sugar before and after operation were approximately the same, although the postoperative curve returned to the fasting level slightly sooner. In the 8 cases in whom glucose tolerance tests were made postoperatively only, the curves likewise revealed no abnormality.

Comparison of the glucose tolerance curves before and after total thyroidectomy in 1 diabetic patient (Case 9, Table 2), and in 1 hyperthyroid patient (Case 10, Table 2), both of whom had angina pectoris, revealed changes which were more striking than those found in the aforementioned group. In Case 9, a patient with frank diabetes controllable by diet, the glucose meal evoked a considerably lesser degree of hyperglycemia after the development of hypothyroidism (Table 2). In Case 10, a patient with mild hyperthyroidism and a decreased sugar tolerance, the response to ingested glucose was distinctly improved after hypothyroidism had been induced (Table 2). In these 2 cases, the glycosuria during the 3 hours following the glucose meal was considerably diminished after total thyroidectomy (Table 2).

Discussion. The effect of thyroid activity on carbohydrate metabolism in diabetic patients has been studied extensively. It is now well recognized that when hyperthyroidism develops in the course of diabetes, the diabetic condition is aggravated, whereas when myxedema develops in the course of diabetes, the diabetic condition may be benefited.[15,16] The beneficial effect of lowering the basal metabolic rate in diabetic patients with hyperthyroidism is striking.[15,16] Wilder and his associates[17] have recently reported that a lowering of the basal metabolic rate from a normal to a subnormal level by practically complete removal of the normal thyroid gland in a young diabetic patient was accompanied by an alleviation in the diabetic condition. Rudy, Blumgart and Berlin[18] have likewise observed a beneficial effect from hypothyroidism induced by total ablation of the normal thyroid gland in a very severe diabetic patient. The alleviation of diabetes when hypothyroidism develops may be largely explicable on the basis of the lowered metabolic rate.[15,19]

Whether hypothyroidism has an appreciable effect on the carbohydrate metabolism of non-diabetic patients has been unsettled, as pointed out above. The results of our investigation indicate that the development of hypothyroidism, following total thyroidectomy, has little effect on the carbohydrate tolerance and the fasting serum sugar level in those patients who have no evident abnormalities of thyroid or pancreatic function prior to operation. Although, after the development of hypothyroidism in this group of patients, the fasting serum sugar concentration and the hyperglycemia following glucose were usually slightly lower than preoperatively

(Tables 1 and 2), the changes seem too slight to be considered definitive in view of the normal intrinsic variability in the blood sugar.

In the patient with diabetes but no thyroid disease (Case 10, Table 2), on the other hand, hypothyroidism induced by total thyroidectomy appeared to increase the carbohydrate tolerance considerably. This is in accord with the clinical observations that when myxedema, spontaneous or induced, develops in the course of diabetes, the diabetic condition may be benefited.[14,17,18] Similarly, in Case 11 (Table 2), a patient with hyperthyroidism and an abnormal glucose tolerance curve before operation, the glucose curve became more nearly normal when hypothyroidism developed. It would appear from our results that if the carbohydrate metabolism is deranged, the development of hypothyroidism has a beneficial effect, whereas if the carbohydrate metabolism is normal, the development of hypothyroidism has no or very little influence upon it. This observation finds a counterpart in the observation of Andersen[16] that if the glucose tolerance in patients with exophthalmic goiter is markedly decreased, subtotal thyroidectomy causes a return toward normal, whereas in those hyperthyroid patients who before operation have a normal carbohydrate metabolism, subtotal thyroidectomy exerts no definite influence.

Summary. 1. The fasting serum sugar concentration was found normal in non-diabetic patients with hypothyroidism induced by total thyroidectomy. The postoperative sugar values tended to be slightly lower than those obtained before total thyroidectomy.

2. The glucose tolerance was normal in non-diabetic patients with induced hypothyroidism. The hyperglycemia produced by the glucose was usually slightly less after total thyroidectomy than preoperatively.

3. One diabetic patient and one patient with hyperthyroidism showed abnormal rises in blood sugar following glucose ingestion before operation; after hypothyroidism was induced, both of these patients showed marked decreases in the degree of hyperglycemia following glucose.

4. Our findings indicate that the carbohydrate metabolism is not significantly influenced by hypothyroidism induced by total thyroidectomy except when a derangement of carbohydrate metabolism is evident prior to operation.

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CARBOHYDRATE METABOLISM IN HUMAN HYPOTHYROIDISM INDUCED BY TOTAL ABLATION OF THE THYROID GLAND.

II. The Blood Sugar Response to Insulin.*

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In the preceding article[1] we have reported that the fasting serum sugar concentrations and the glucose tolerance curves are normal in non-diabetic patients with hypothyroidism induced by total ablation of the thyroid gland. As compared with the values observed before thyroidectomy, the fasting serum sugar concentration tended to be slightly decreased and the glucose tolerance tended to be slightly increased after hypothyroidism had developed.[1]

We have been unable to find any studies in the literature concerning the influence of hypothyroidism upon sensitivity to insulin in man; on the other hand, experimentation both in diabetic and non-diabetic animals has resulted in the opinions that the sensitivity to insulin after removal of the thyroid gland is either increased[2,3] or unchanged.[4] In this paper we report the blood sugar response of non-diabetic patients to the subcutaneous injection of 20 units of insulin before and after the development of hypothyroidism induced by total ablation of the thyroid gland. It has been possible to follow closely the development and extent of the hypothyroid state by observations of the clinical picture, the basal metabolic rate, the serum cholesterol concentration and other related measurements.[5]

* This investigation was aided by a grant from the William W. Wellington Memorial Research Fund of Harvard University.

Methods. The subjects of this study were patients with chronic intractable heart disease who, before total thyroidectomy, showed no evidences of diabetes or hyperthyroidism. Total ablation of the thyroid glands was performed for its beneficial effect on congestive heart failure or angina pectoris, in accord with the considerations of Blumgart and his associates.[6] None of the patients was particularly malnourished and each of them received a diet adequate in carbohydrate for several weeks before the response to insulin was studied. The ages varied from 22 to 58 years.

Total thyroidectomy was performed according to the technique of Berlin[7] and hypothyroidism developed in every instance. The blood sugar concentration was measured by the method of Folin and Wu.[8] Basal metabolic rate measurements were made the same day or within a few days of the insulin studies; the measurements were made in duplicate with a Collins Benedict-Roth apparatus and calculated according to the Aub-DuBois normal standards.[9] After obtaining a sample of venous blood from the patient in the postabsorptive state, 20 units of insulin (Lilly) was injected subcutaneously and samples of venous blood were drawn ½, 1, 1½, and, at times, 2 hours after the injection. In each patient the blood pressure, pulse and general appearance were watched closely for the development of signs of insulin reaction. In several instances the experiment was terminated after 1½ hours because the patient was distressed. At the termination of each test the patient was given 500 cc. of orange or pineapple juice.

Results and Discussion. The blood sugar response to 20 units of insulin injected subcutaneously was measured in 6 subjects before, and at intervals after total ablation of the thyroid gland. In 7 additional patients studies were made only after hypothyroidism had developed. The blood sugar changes following insulin, together with the basal metabolic rate values, are given in Table 1. At the time of the earliest post-operative measurements, made from 2 or 3 weeks after operation, the basal metabolic rates had shown characteristic decreases (Table 1), but the clinical picture of hypothyroidism was not present. When tests were performed from one month to 1 year after operation, clinical evidences of hypothyroidism, varying from mild signs and symptoms to marked myxedema, were manifest, the basal metabolic rates were low (Table 1) and the serum cholesterol concentrations, measured in several cases, were elevated.

In the 6 patients studied before and after operation, the post-operative blood sugar response to insulin, regardless of the degree of hypothyroidism present, was essentially the same as that obtained before operation. The average maximum decrease in blood sugar following the subcutaneous injection of 20 units of insulin in these 6 patients before operation was 34%; the average maximum decrease in these same patients after the development of hypothyroidism was likewise 34%. The average basal metabolic rate before operation was −3% and after operation was −22%.

The blood sugar response to insulin in the 7 patients studied only postoperatively showed no correlation with the degree of hypothyroidism and was similar to that observed both before and after operation in the previous group of patients. The average maxi-

mum decrease in blood sugar in these 7 patients was also 34%; the average basal metabolic rate was −25% (Table 1).

TABLE 1.—HUMAN TOLERANCE TO INSULIN IN HYPOTHYROIDISM, INDUCED BY TOTAL THYROIDECTOMY.

Case No.	Age.	Pre-operative diagnosis *	Time of study.	Basal metabolic rate (deviation from average normal), %	Blood sugar changes with 20 units insulin.				
					Fasting (before insulin), mg. per 100 cc.	Time after insulin.			Maximum blood sugar decrease, %
						60 minutes, mg. per 100 cc.	90 minutes, mg. per 100 cc.	120 minutes, mg. per 100 cc.	
1	42	A. P.	Before op.	− 7	81	52	..	52	35
			3 wks. post-op.	−29	80	61	..	50	37
2	41	A. P.	Before op.	+ 8	85	56	54	50	40
			3 wks. post-op.	−15	83	54	54	..	40
3	45	C. H. F.	Before op.	− 6	117	95	70	70	40
			4 wks. post-op.	−24	90	67	66	..	26
4	45	C. H. F.	Before op.	+ 9	100	83	74	..	26
			3 wks. post-op.	−20	96	84	74	74	23
			6 wks. post-op.	−24	102	66	64	64	37
5	36	C. H. F.	Before op.	−14	75	61	..	54	28
			2 wks. post-op.	−17	78	62	65	54	31
			5 wks. post-op.	−21	75	66	54	59	28
6	58	C. H. F., A. P.	Before op.	− 7	100	69	67	..	33
			3 wks. post-op.	−16	76	62	54	50	34
7	31	C. H. F.	8 wks. post-op.	−11	75	55	57	..	24
8	22	C. H. F.	5 mos. post-op.	−19†	80	71	..	50	37
9	18	C. H. F.	4 mos. post-op.	−36	85	80	68	60	23
10	46	A. P.	4 wks. post-op.	−20	91	80	65	..	28
11	52	A. P.	2 wks. post-op.	−24	95	72	61	..	35
			4 mos. post-op.	−40	95	80	67	64	33
12	34	C. H. F.	4 wks. post-op.	−35	85	54	49	..	42
			3 mos. post-op.	−31	91	83	49	..	46
13	42	C. H. F.	1 yr. post-op.	−16	95	54	51	..	46
14	51	A. P., H., D.	Before op.	+20	100	95	72	70	30
			2 wks. post-op.	−18	87	59	53	..	27
			4 wks. post-op.	−33	114	58	61	58	50

* A. P. signifies angina pectoris; C. H. F., congestive heart failure; H., mild hyperthyroidism, and D., mild diabetes.

† This patient was receiving small doses of thyroid (½ grain daily, Armour's) to obviate untoward symptoms of myxedema.

The blood sugar response to insulin was also studied before and after total ablation of the thyroid gland in 1 patient with mild diabetes and mild hyperthyroidism (Case 14, Table 1). Before operation, when the basal metabolic rate was +20, the maximum decrease in blood sugar following the injection of 20 units of insulin, was 30%; after operation, when the basal metabolic rate was −33%, the maximum decrease was 50%. In view of the range of maximum

blood sugar decreases after insulin observed by us in our other patients (Table 1) and by others [10,11] neither the pre-operative nor the post-operative decrease in this patient can be considered abnormal.

The lowest blood sugar values obtained after the injection of 20 units of insulin varied from 49 to 70 mg. per 100 cc. of blood. At these concentrations of blood sugar, approximately one-half of the patients showed some characteristic signs and symptoms of hyperinsulinism. The earliest symptoms usually were weakness and a sensation of being "light-headed." Hunger and thirst were rarely found, even though each patient was questioned closely concerning these symptoms. The heart rate and the blood pressure showed no appreciable changes, probably because the amount of insulin used was insufficient to induce marked reactions.[12] The patients with moderate to marked hypothyroidism showed the same signs and symptoms of hyperinsulinism at approximately the same level of blood sugar as did the patients before total thyroidectomy, when the basal metabolism was normal.

The average maximum decrease in blood sugar following the injection of 20 units of insulin in our patients coincides with the average maximum decrease in blood sugar observed by Fletcher and Campbell[10] following the injection of the same amount of insulin in 5 normal individuals.

The above observations, showing that the development of hypothyroidism does not increase sensitivity to insulin in man, differ from the results of several investigators who found that insulin sensitivity in rabbits was increased many fold after thyroidectomy.[3,13] Studies in thyroidectomized animals are at times difficult to interpret because of the inability to maintain and evaluate the degree of hypothyroidism. Total ablation of the thyroid gland in human subjects, however, causes persistent hypothyroidism[7] which can be evaluated satisfactorily by basal metabolic rate and serum cholesterol measurements, and by clinical observations.

It has been quite definitely established that there is essentially no ability to counteract the effect of insulin in adrenalectomized and in sympathectomized animals.[14,15] The finding of a normal blood sugar decrease following insulin in our patients after total thyroidectomy indicates that the response of the sympathetico-adrenal system to insulin in these patients with hypothyroidism is normal. Furthermore, our results indicate that there is no antagonism between the internal secretions of the normal thyroid gland and that of the pancreas. The favorable influence of hypothyroidism upon diabetes[16,17,18] would appear, therefore, to be related to other factors in carbohydrate metabolism.

Summary. 1. The sensitivity to insulin has been observed in non-diabetic, non-hyperthyroid patients before and after the development of hypothyroidism induced by total ablation of the thyroid gland.

2. In these patients no appreciable difference has been found in the average maximum decrease of blood sugar following the subcutaneous injection of 20 units of insulin before and after hypothyroidism developed. The average decrease in blood sugar in all studies following the injection of 20 units of insulin was 34%.

3. Signs and symptoms of mild hyperinsulinism were manifest in patients with hypothyroidism at the same level of blood sugar as in patients with normal metabolic rates.

4. Our results indicate that the response of the sympathico-adrenal system to insulin is normal in these patients with hypothyroidism, and that there is no antagonism between the internal secretions of the normal thyroid gland and of the pancreas.

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MULTIPLE PARATHYROID TUMORS WITH MASSIVE MEDIASTINAL AND SUBCUTANEOUS HEMORRHAGE.

A Case Report.

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In the past few years parathyroid tumors, with the characteristic manifestations that usually accompany them, have become a well-established clinical entity. Until recently, however, no distinction

has been drawn between cases of single and multiple parathyroid enlargement. Albright, Bloomberg, Castleman and Churchill[1] have now shown that the histologic appearance of the two types is quite different and have suggested that the two types may be etiologically distinct. In the multiple enlargement type the tumor cells are uniformly of the large, clear ("wasserhell") variety; while the histologic picture of the single tumor case presents a diversity of cell types and cell sizes. At present, there is no satisfactory clinical method of distinguishing between these two groups.

Because examples in the literature of multiple parathyroid tumors are rare and because of the extremely unusual clinical picture presented, it seems of value to report the following case:

Case Report. A 50-year-old white, married, male, Lithuanian textile worker entered the hospital on October 3, 1933, because of a "sore throat" with progressive swelling of his neck of 4 days' duration. On account of language difficulties the *history* obtained was scanty and unreliable.

Previous to the present complaint the patient had apparently been well except for some progressive weakness during the 5 weeks before admission. For a week preceding the onset of his "sore throat" he had been on a heavy drinking spree which was terminated by a short attack of delirium tremens.

Four days before admission he developed a sore throat without fever, accompanied by a diffuse, painless swelling of the neck. As the swelling gradually became worse he noticed increasing difficulty in swallowing, as well as in breathing and talking. He had a slight cough productive of small amounts of yellow sputum. Occasionally there were mild headaches and spells of dizziness.

The day before admission he noticed a large "bruised" area on the anterior aspect of the right chest and neck. No history of trauma could be obtained. On admission the swelling had extended to his face and he was able to take only fluids by mouth, and these with difficulty.

The *family history* was irrelevant. The patient had for years drunk an excess of alcohol. The *past history* revealed that he had frequent colds and sore throats following his alcoholic sprees. Recently there had been slight dyspnea on exertion.

The *physical examination* revealed a well-developed and rather obese middle-aged man who was sitting up in bed acutely ill. He was in moderate respiratory distress and was very nervous, complaining frequently of double vision. The skin of the face and neck was of an unusual reddish-blue color, as if congested. There was slight edema of the face and cyanosis of the lips; the conjunctivæ were moderately injected; the tonsils were markedly enlarged but there was no exudate. The entire pharynx, soft palate and tonsillar region were of a reddish-purple color due to multiple minute hemorrhages and to congestion with blood. In the retropharyngeal region was a marked swelling which appeared to be due to a large hematoma.

The neck, especially the anterior aspect, was diffusely and markedly enlarged. Palpation revealed no lymph-node enlargement or masses except for an indefinite firmness in the midline, extending beneath the manubrium. There was only slight tenderness and slight pitting. No abnormal pulsation, no bruit, nor any evidence of collateral circulation was made out.

Over the anterior aspect of the right chest extending down to the nipple was a large ecchymotic area which pitted moderately on pressure (Fig. 1). Percussion showed definitely increased retromanubrial dullness, especially to the right, and also dullness posteriorly over both lung apices, extending 2 to 3 inches below the scapular spines. Decreased breath sounds with

some bronchial breathing were heard over these latter areas but no râles were detected. Tactile fremitus was diminished. The remainder of the lung was clear. There was no apparent cardiac enlargement. The heart sounds were distant but of good quality and there were no murmurs. The pulse rate was 84 per minute and regular. Blood pressure in the right arm was 140 mm. Hg systolic and 96 diastolic, while in the left the systolic was 160 and the diastolic 110. Abdominal examination was negative except that the liver was palpable for 3 cm. below the costal border.

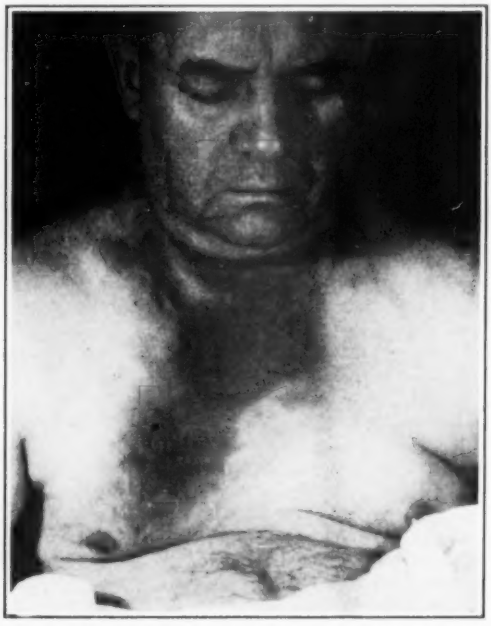

FIG. 1.—Appearance of the patient on admission. Note the discoloration of the face, swelling of the neck, and the large ecchymosis on the chest.

Laboratory Examinations. Red cell count, 4,790,000; hemoglobin, 12.64 grams per 100 cc. A blood smear showed the red cells to be normal. The white count was 11,600 (68% neutrophils, 16% lymphocytes and 16% monocytes). The platelets, bleeding time and the clotting time of the blood were all found to be normal.

Four urine specimens and one stool were normal. The sputum contained no blood or acid-fast organisms. Roentgen ray examination of the chest was interpreted as showing "a rounded tumor mass in the superior mediastinum and rising above the clavicles" (Fig. 2). This picture was thought to be consistent with aneurysm or some other mediastinal tumor.

The patient's *course* in the hospital was one of progressive decline. His temperature varied between 97° and 99° F.; respirations between 15 and 25 per minute. Because of extreme restlessness he was given sedatives freely. His general condition, however, gradually became worse and his breathing became extremely labored. Finally, on the 4th day following admission, he developed delirium tremens, his pulse became thready and he died shortly thereafter.

The clinical diagnosis was mediastinal tumor, with hemorrhage into the

tumor and subcutaneous tissues. The tumor was thought to be either a neoplasm or an aneurysm. *Necropsy* (performed 10 hours postmortem by Dr. Soma Weiss): *Grossly*, the body showed only what was noted on physical examination. On making an incision over the thorax, blood was found to ooze diffusely from the tissues. All the anterior thoracic muscles and the anterior mediastinum around the base of the heart were infiltrated with blood. The pericardium and heart were normal, except for slight mitral thickening. The aorta was soft and elastic, and was without lesions of any kind. The lungs showed slight basal congestion.

On each side of the trachea at the level of the clavicle a nodule was found. The larger one on the right measured 7.0 by 3.5 by 2.1 cm. and weighed 22 grams. It was ovoid in shape, fluctuant and well encapsulated. On incision it was found to be filled with blood which could be seen dissecting the tumor tissue through the capsule. From this point, blood could be traced to all the subcutaneous and mediastinal hemorrhagic areas. The cut surface of the nodule was pale brownish-gray with many hemorrhagic areas of varying size. The tissue was of a very soft consistency. The mass on the left side was smaller, weighing 13.6 grams and measuring 2.4 by 3.5 by 2.1 cm. In shape and appearance and on section it was exactly similar to the other tumor except for the absence of hemorrhage.

The thyroid was not remarkable. No normal parathyroids were seen grossly. The liver (wt. 2200 gm.) was rather soft and friable, and light yellow in color on cross section. The intestines, adrenals, kidneys, spleen and pancreas were all essentially normal.

Anatomical diagnosis: parathyroid adenomata (made from frozen sections), hemorrhage into one tumor with suffusion of mediastinal tissues and muscles of the neck and thorax, fatty infiltration of the liver, and slight mitral valvulitis.

The *histologic examination* of the heart, pancreas, adrenals and testes was essentially negative. The lungs and spleen showed congestion. In many organs were seen occasional clumps of orange-yellow pigment giving a positive test for iron. Most of the liver cells were vacuolated and in the cytoplasm of a few of the periportal liver cells irregular, red-staining masses were visible.

The renal tubules were moderately distended and contained coagulated albumin. In the cortex, the tubular epithelium presented swollen, clear cytoplasm. Throughout, small patches of sclerosis were also seen. Sections of bone from the vertebral bodies, the ilium and the femur failed to disclose any abnormality.

The appearance of the tissue from both parathyroid tumors was essentially the same (Fig. 3). Masses of medium-sized cells were found with rather clear cytoplasm, small round or oval dark-staining nuclei, and well-defined cell margins separated by fine connective-tissue trabeculations. For the most part, the cells were loosely arranged and frequently occurred in cord-like masses. There were areas of hemorrhage and rare small islands of fat tissue. Capillary bloodvessels were numerous and occasional clumps of orange-yellow pigment were found. There were rare cyst-like spaces filled with a homogeneous pink-to-bluish staining material. No mitotic figures were detected. The absence of fat in the large clear cells was demonstrated by the fact that they did not stain with Scharlach R. In the same cells Best's carmine stain revealed small droplets of glycogen. The capsule was well defined and partly covered with an organizing blood clot. In the tissues of the neck a small parathyroid gland was discovered during the microscopic examination. The cells were all of the same large, clear type as those composing the two tumors.

The supplementary microscopic diagnoses were hyperplasia of the parathyroids, alcoholic cirrhosis and hemosiderosis of the spleen, liver, adrenals and bone marrow.

Comment. From a diagnostic standpoint this patient presented on admission a most unusual and interesting picture. Clinically, the involvement of the face and neck with diffuse cutaneous hemorrhage and swelling, accompanied by dysphagia and dyspnea, seemed best explained by assuming the presence of both a large infiltrating hemorrhage and a superior mediastinal obstruction. Roentgen ray and physical examination suggested the presence of a superior mediastinal mass which was obviously causing the obstruction and was probably the source of the hemorrhage. The true nature of the tumor was not recognized even at autopsy until frozen sections had been examined. It should be mentioned in passing that a somewhat similar appearance of the head and neck is seen in two conditions besides an actual hemorrhage, namely, so-called "traumatic cyanosis,"[2,3] and rupture of a mediastinal aortic aneurysm into the superior vena cava.[4]

Massive subcutaneous and interstitial hemorrhage from a parathyroid tumor such as occurred in this case has not been previously reported in the literature. Petechial hemorrhages into the parathyroid glands are occasionally seen in infants with tetany,[5,6] but in such cases the bleeding occurs under quite different circumstances from that of the patient under discussion, and so is not comparable.

Histologically both tumors were almost identical with those reported by Albright and his coworkers.[1] It should be noted that the normal-sized parathyroid gland, recognized only on microscopic examination of the tissues of the neck, was found to have a histologic appearance similar to that of the tumors themselves. As no other parathyroids were discovered in spite of a careful search, it must be concluded that all of this patient's parathyroid tissue was in the same abnormal state.

In the absence of chemical blood studies no definite conclusions can be drawn in regard to the state of the calcium and phosphorus metabolism. Postmortem Roentgen rays of the entire skeleton, however, as well as histologic examination of several bones, revealed no decalcification or cysts. The postmortem bladder urine contained 3.18 mg. per 100 cc. of calcium and 0.506 mg. per 100 cc. of phosphorus,* and had a specific gravity of 1.030. Although these figures are essentially normal,[7,8,9] the urine was obtained under such uncontrolled conditions that the results are only moderately significant. Thus in this case we have no evidence of hyperfunction of the parathyroids; but because it has been shown[10,11] that even with normal kidneys bone changes are not necessarily present, it is impossible to state that in this case there was no hyperparathyroidism.

Summary. A case is reported of multiple parathyroid tumors with massive mediastinal and subcutaneous hemorrhage arising spontaneously from one—a complication not previously recorded. The patient had no symptoms or signs of hyperparathyroidism but

* Analyses kindly performed by Dr. F. Albright.

FIG. 2.—Roentgenogram of the thorax. Note the bilateral superior mediastinal masses.

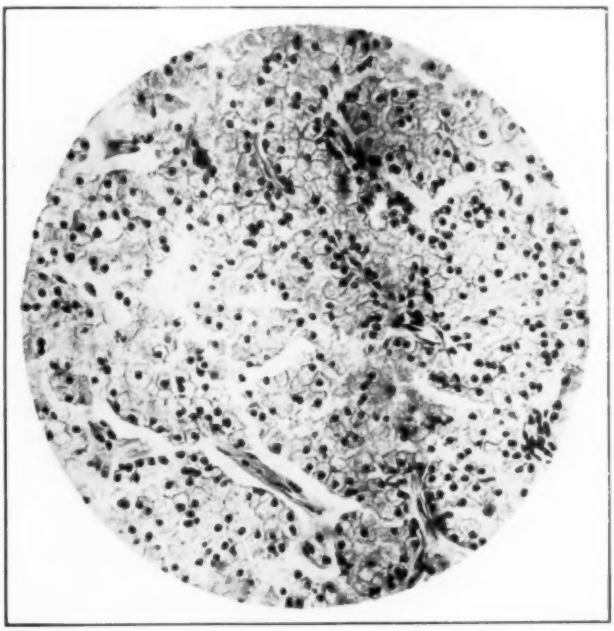

FIG. 3.—Typical section from one of the parathyroid tumors. Note the uniform type of large clear cell, and the tendency to gland formation.

no calcium or phosphorus determinations on the blood were made. His complaints were entirely related to the hemorrhage. All the parathyroid tissue examined proved to be histologically identical with that of the cases of multiple parathyroid tumor recently reported by Albright and his coworkers.

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THE CAUSES OF COMA IN PATIENTS ENTERING A GENERAL HOSPITAL.*

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The great frequency with which patients are brought to a general hospital in coma is not fully appreciated. There were 37,438 entries in this hospital in the year 1933. (These do not include entries to the South Department for contagious diseases.) Of these, 1167, approximately 3%, entered in coma. These figures are startling and obviously do not apply to all hospitals, for city hospitals doubtless receive a higher proportion of patients in coma than do other hospitals. The present paper is concerned with the relative frequency of the various causes of coma as a presenting sign as an aid to accurate diagnosis and immediate treatment. The records of all patients who entered this hospital in 1933 were examined† and those in which coma was mentioned as a presenting sign were analyzed. Many of these patients, including all with a doubtful diagnosis, were personally seen by one or the other of the authors in their capacity as neurologic consultant.

* The authors wish to express their appreciation of Dr. Stanley Cobb's invaluable advice and assistance in the course of this work.

† We wish to express our indebtedness to Mary S. Aring for her diligence in carrying out this part of the work.

Among the various causes of coma there are some which require emergency treatment to save life, for example, diabetes, hyperinsulinism, poisoning, traumatic shock, exsanguination, subdural hematoma, brain tumor, meningitis and eclampsia. The importance of immediate diagnosis when the coma is of unknown origin is evident. Making diagnosis more difficult is the fact that patients in coma frequently enter the hospital without a history (68% of the authors' 1167 cases).

A knowledge of the more common causes of coma as a presenting sign, and the relative frequency of these causes, would obviously be helpful in making the diagnosis. The literature contains very little statistical data of this sort. Camauer[1] published an analysis of 26 cases, of which 8 proved to be cerebral hemorrhage, 5 uremia, 3 trauma, 2 eclampsia, 2 cardiac insufficiency, 1 endarteritis obliterans luetica, 1 cerebral neoplasm, 1 thrombosis, 3 unknown causes. Bissell and Le Count[2] analyzed the cause of death in 400 cases of patients who died in coma, and Holcomb[3] continued this analysis with 346 more cases. Because only 22.5% of the 1167 cases of our series ended fatally, and because many cases develop coma in the hospital as a terminal state, Bissell and Le Count's and Holcomb's statistics are not applicable to the problem of coma as a presenting sign. The textbooks are of little assistance. They mention many causes of coma and discuss at length some that are rare, while others that are more common they do not include at all. They do not attempt to give any idea of the relative frequency of the various causes.

TABLE 1.—CAUSES OF COMA AS A PRESENTING SIGN AND THEIR MORTALITY.

Disease.	Number of cases.	Per cent total comas.	Per cent non-alcoholic comas.	Cases of group ending fatally.	Per cent of group ending fatally.
Alcohol	690	59.1	..	14	2.0
Trauma	152	13.0	32.0	48	31.5
Cerebral vascular lesions	118	10.1	24.7	91	77.1
Poisoning	33	2.8	7.0	3	9.0
Epilepsy	28	2.4	6.0	0	0.0
Diabetes	20	1.7	4.2	11	55.0
Meningitis	20	1.7	4.2	20	100.0
Pneumonia	20	1.7	4.2	18	90.0
Cardiac decompensation	17	1.4	3.5	12	70.6
Exsanguination	10	0.9	2.1	10	100.0
Central nervous system syphilis	7	0.6	1.4	0	0
Uremia	7	0.6	1.4	7	100.0
Eclampsia	7	0.6	1.4	3	42.8
Miscellaneous	38	3.2	8.0	26	68.4
Total	1167	100.0	100.0	263	22.5%

The 1167 cases discussed below represent unselected serial cases entering the hospital with coma as a presenting sign. Table 1

gives the various causes of coma in these cases. Fig. 1 illustrates the relative frequency of these causes.

Alcoholism (690 cases, 59.1% of total cases of coma; mortality in this group, 2%). The proportion of alcoholics entering the Boston City Hospital is undoubtedly greater than the proportion entering the average hospital, because "drunks" from all parts of the city are brought here. Most of the records of alcoholic patients are inadequate. The data gathered on alcoholic coma are, therefore, subject to error. There were 2079 admissions for alcoholism in the year 1933 (6% of the total admissions). The records of 690 of these (33%) mentioned coma as a presenting sign. Many of these comatose alcoholics also had injuries. There were minor head injuries in 80; minor injuries elsewhere on the body in 16

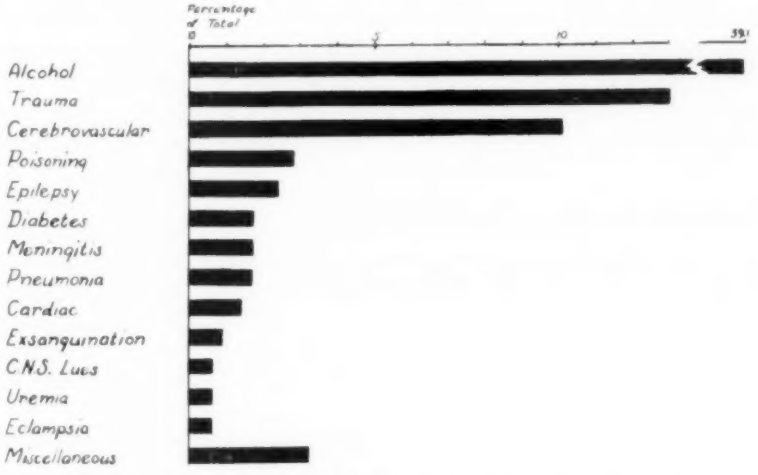

FIG. 1.—Causes of coma on admission to the hospital, 1167 cases.

In these cases coma was listed as being of alcoholic origin, although it is possible that injury played some part in its causation. Where alcoholism was associated with severe head injury, such as a fractured skull, contused or lacerated brain, or extradural or subdural hemorrhage, the coma is listed under head injuries and alcohol is considered as a secondary factor. Alcohol was a secondary factor in 26 cases of severe head injury and in 6 cases with other causes of coma; 62% of all the coma cases had alcoholism as either a primary or a secondary factor.

Trauma (152 cases, 13% of total cases of coma; mortality in this group, 31.5%). Among the traumatic comas, injuries to the head were by far the most common cause (Table 2). In a few cases, injuries to the chest, pelvis or spinal cord produced coma. Among the head injuries there was a relatively high proportion of subdural

and extradural hemorrhages. The other head injuries have been classified according to the extent of injury to the brain (Munro[4]) as judged by the period of unconsciousness, the character of the spinal fluid, other physical findings, such as bleeding from the ear, the subsequent course in the hospital and in some cases by postmortem findings. The high proportion of severe brain injuries and of skull fractures is understandable, since the cases here considered are head injuries that enter the hospital in coma.

TABLE 2.—COMA DUE TO TRAUMA.

Type.	Number of cases.	Per cent of total head injuries.	Cases with fractured skull.	Per cent with fractured skull.
Concussion	17	12	0	0
Edema of brain	20	15	3	15
Contusion of brain	38	28	9	24
Lacerated brain	47	34	41	87
Subdural hemorrhage	12	8	4	33
Extradural hemorrhage	3	3	2	67
Total head injuries	137	100	59	43
Chest injury	7			
Pelvis injury	4			
Spinal cord injury	4			
Total	152			

TABLE 3.—COMA DUE TO CEREBRAL VASCULAR LESIONS.

Type.	Number of cases.	Per cent of cerebral vascular lesions.
Hemorrhage	49	42
Thrombosis	29	25
Hypertensive and arteriosclerotic encephalopathy	10	8
Embolus	5	4
Primary subarachnoid hemorrhage	4	3
Undetermined	21	18
Total	118	100

Cerebral vascular lesions (118 cases, 10.1% of total coma cases; mortality in this group, 77.1%). After alcoholism and trauma, cerebral vascular lesions are by far the most common cause of coma as a presenting sign (24.7% of the non-alcoholic group). In analyzing the types of cerebral vascular lesions (Table 3), we find that cerebral hemorrhage is most common. We have not accepted this diagnosis unless the history and physical findings were corroborated either by autopsy evidence or the presence of gross blood in the spinal fluid. There is reason to suppose (Merritt and Aring[5]) that in cerebral vascular lesions with or without coma, cerebral thrombosis is more common than cerebral hemorrhage. The presence of coma as a presenting sign favors the diagnosis of hemorrhage as against thrombosis, while the absence of coma is in favor of thrombosis. There were 4 cases of cerebral emboli, and 4 of pri-

mary subarachnoid hemorrhage. In 21 of our cases where the diagnosis of cerebral vascular injury was quite clear because of the history and physical findings, there was not sufficient evidence to determine the type of injury. In 10 cases the diagnosis of encephalopathy on the basis of hypertension, arteriosclerosis, or both, was made clinically. The so-called "cerebral vascular spasms" would fall into this group.

Poisoning (33 cases, 2.8% of total cases of coma; mortality in this group, 9%). Acute poisoning (non-alcoholic) was the fourth most common cause of coma in this series. Of 33 cases, 16 were caused by barbital or its derivatives, 12 by carbon monoxid, 1 each by bromid, permanganate, nitrobenzin, lysol and sodium nitrate. The patient who took lysol died, as did also the patient who took nitrobenzin and one who took barbital.

Epilepsy (28 cases, 2.4% of total cases of coma; mortality, 0). This number of patients entering the hospital in coma following an epileptic seizure is probably not unusual for a city hospital. Of the 28 cases recorded here, 2 represent the same patient on different entries. Several of the others had been admitted in the same condition in previous years.

Diabetes (20 cases, 1.7% of total cases of coma; mortality in this group, 55%). Diabetic coma is not yet rare. Of the 20 cases in our series, 3 represent the same patient on different admissions. All but 7 of these cases were known diabetics, in whom the coma was precipitated by infections or indiscretions in diet. There were 3 with acute upper respiratory infection, 3 with bronchopneumonia, 2 with abscesses, 2 with gangrene of the foot, 1 with an infected bedsore and 2 had overstepped dietary limitations. Of the remaining 7 cases, 1 had an acute suppurative parotitis; the others were uncomplicated.

Meningitis (20 cases, 1.7% of total cases of coma; mortality in this group, 100%). It is not generally realized that meningitis is as common a cause of coma as diabetes among hospital entrants. Of the cases reported here, the organism was the pneumococcus in 9, the tubercle bacillus in 4, the meningococcus in 2, the streptococcus in 2, the staphylococcus in 1 and the organism was not identified in 2.

Pneumonia (20 cases, 1.7% of total cases of coma; mortality in this group, 90%). Pneumonia is not mentioned in the textbooks as one of the diagnoses to be considered in cases in which coma is a presenting sign. Yet pneumonia is 3 times as common as uremia in our series. Of our 20 cases, 13 were bronchopneumonia and 7 were lobar pneumonia. Ten of the 18 fatal cases died within 24 hours after admission.

Cardiac decompensation (17 cases, 1.4% of total cases of coma; mortality in this group, 70.6%). There were 17 patients of the total group studied who entered the hospital in coma because of

cardiac decompensation. This cause of coma is also little appreciated. As in the pneumonia comas, many of these patients were moribund; 8 of the 12 fatal cases died within 24 hours after admission. Coronary thrombosis was the cause of the attack in 5 cases, 2 had rheumatic, 1 hypertensive and 9 arteriosclerotic heart disease.

Exsanguination (10 cases, 0.9% of total cases of coma; mortality in this group, 100%). In 4 of these cases the bleeding was due to injury, the hemorrhage being external in 2 and internal in 2. Of the remaining 6 cases, in 2 the bleeding was due to rupture of an esophageal varix in conjunction with cirrhosis of the liver, in 2 to carcinomatous erosion in the gastro-intestinal tract, in 1 to the rupture of an aortic aneurysm, and in 1 to a tuberculous hemoptysis.

Central Nervous System Syphilis (7 cases, 0.6% of total cases of coma; mortality, 0). In the cases of coma due to syphilis of the central nervous system, all had had repeated attacks of unconsciousness, usually with convulsions. In 3 there was evidence of parenchymatous involvement, and the diagnosis of dementia paralytica was made.

Uremia (7 cases, 0.6% of total cases of coma; mortality in this group, 100%). The relatively few cases of uremia in our series surprised us. Many more patients develop uremic coma terminally while on the wards. It would seem that kidney insufficiency in most instances is gradual enough in onset and produces enough symptoms to bring the patient to the hospital before coma supervenes.

Eclampsia (7 cases, 0.6% of total cases of coma; mortality in this group, 42.8%). In 6 of these cases there had been convulsions before entry. In the seventh there had been severe intractable vomiting and toxic hepatitis was found at autopsy.

Miscellaneous (38 cases, 3.2% of total cases of coma; mortality in this group, 68.4%). There are many miscellaneous causes of coma. In our series these were: Erysipelas, 4; burns, 4; encephalitis, 3; brain tumor, 3; miliary tuberculosis, 2; carcinomatosis, 2; and 1 each of hypoglycemic shock (insulin), Stokes-Adams' disease, immersion, syncope, Simmonds' disease, Friedreich's ataxia, rupture of membranous urethra, pernicious anemia, hysteria, ruptured ectopic pregnancy, leukemia, cholemia, strangulated hernia, septicemia and empyema. In 5 cases a diagnosis could not be made. In many of these the coma was doubtless terminal. The rarity of cholemia, Stokes-Adams' disease, syncope and hysteria as causes of admission coma is noteworthy.

The 3 cases listed as encephalitis include 1 in which the symptoms followed shortly after an injection of vaccine, type unknown. In this case paralysis of all extremities and high fever soon led to coma and death. The second encephalitis case had its onset 7 years before, following measles. The patient had frequent attacks of coma following this, and was admitted in one such attack. The third was a boy, aged 14, who had had an upper respiratory infec-

tion for 2 weeks and entered after several convulsions. He remained mentally cloudy for 2 weeks, had high fever, diplopia and unequal pupils, but finally recovered. The patient with Simmonds' disease lapsed into coma in which he remained for 3 days, and then recovered. The patient with Friedreich's ataxia had an unexplained coma from which she also recovered. The patient with the ruptured membranous urethra had apparently incurred his injury 10 days previously when sounds were passed to dilate his urethral stricture. He entered with massive urinary extravasation and gangrene of the periurethral tissue and abdominal wall.

Summary. The records of 37,438 patients who entered the Boston City Hospital in 1933 were examined, and it was found that 1167 patients entered in coma. These cases were analyzed and the diagnoses eventually arrived at are tabulated and discussed. Of these 1167 cases, alcohol was responsible in 59.1%; trauma, in 13%; and cerebral vascular lesions in 10.1%. The last two made up more than one-half of the non-alcoholic comas. Other causes, each forming 3% or less of the total, in order of numerical importance were: poisoning, epilepsy, diabetes, meningitis, pneumonia, cardiac decompensation, exsanguination, syphilis of the central nervous system, uremia and eclampsia.

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SPONTANEOUS HEMOPHILIA.

REPORT OF SIX CASES IN BROTHERS.

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HEMOPHILIA is now generally regarded as an hereditary constitution, sex-linked and recessive. The factor for its inheritance is thought to be carried on one of the sex chromosomes, there being 2 such chromosomes in the human female and 1 in the male. In the male, in place of 1 X chromosome we are thought to have an altered chromosome, usually called *Y*. If hemophilia is a recessive character, the descent of the factor can be represented thus:

	Female.		Male.	
Parent	**X** X		X Y	
Offspring	**X** X	X X	**X** Y	X Y

From this it is seen that the affected X chromosome passes to 50% of male and female offspring; but in the female its effect is apparently offset by the presence of a normal X chromosome, and she thus escapes the symptoms of the disease. The daughters of hemophilic males are carriers, but the sons are not affected. From this it follows that the immediate inheritance of all hemophilic males must be from the mother. Theoretically, as a result of crossing a female carrier with a bleeder, one-half of the male offspring should be bleeders. The females of such parents should be half carriers and half hemophilic females. As no authentic case of hemophilia in a woman has been described, it has been suggested that such a combination may be incompatible with life. This is not the case, however, in the analogous hereditary condition of color blindness.

Hemophilia occasionally does appear with no known ancestral bleeders. It is then referred to as sporadic or spontaneous hemophilia. The origin of these cases has been the subject of much speculation. Actually, the explanation of these spontaneous hemophilias resolves itself to 3 definite possibilities: (1) That these cases arise *de novo*, and that the laws of transmission remain the same as in the usual type of this disease. This conception assumes sudden hereditary change which breeds true (often miscalled mutation).*[11] (2) Long inheritance through the females with the males not showing hemophilia to the extent expected by the law of averages. This implies inherited constitutions coming from remote individuals far beyond the reach of the investigator, and that by chance alone the recognized males of such families have failed to receive the hereditary materials which cause the increased susceptibility to bleeding. This is in agreement with Bullock and Fildes[4] (1911), who pointed out that skipping of generations probably does not occur, and designated such males as did occur in these families "as unaffected males." They further stated that they did not believe that the disease could arise *de novo*. (3) There is the error in the study of the genealogic tree, due to illegitimacy. The difficulties of investigation along this line are obviously almost insurmountable. It may be done by study of the blood groups. However, even in the rare instances where both maternal grandparents are available, in only about 50% of the cases would it be possible to demonstrate an existing error in the paternity of the mother.

The earliest report of cases of what was apparently genuine spontaneous hemophilia (blood studies were not introduced until 1901) was by Stoehr[13] (1850), in which he reported 3 cases of bleeding with no other bleeder males in 3 previous generations.

For similar cases see Table 1, in addition to which there were

* Professor Oertel, in his Outlines of Pathology, points out that the original meaning of the word was gradual and directional, rather than sudden change.

many others who reported cases that, due to inaccuracies or insufficient data, could not be definitely established as genuine hemophilia.

TABLE 1.—REPORTED CASES OF SPONTANEOUS HEMOPHILIA.

Author	Date.	No. of bleeders.	No. of generations without bleeders.	Remarks.
Stoehr[13]	1850	3	3	
Grandidier[7]	1855	5	3	
Barlow[3]	1876	2	2	
Hansen,[8] *a*	1886	4	2	
Hansen,[8] *b*	1886	5	2	
Ripke[12]	1889	1	3	
Kinnicutt[9]	1905	1	4	
Albers[1]	1906	1	3	
Weil[15]	1908	1	3	
Thompson[14]	1911	5	4	
Gettings[6]	1911	5	3	Extensive study of all collaterals.
Arrigoni[4]	1932	1	3	
Laclette[10]	1932	1	?	
Fonio[5]	1933	2	2	

It is in the examples where several children of a family apparently spontaneously develop the disease that particular interest lies, for in them it seems quite certain that the disease does not arise *de novo*, but that they must have inherited the disease from the recessive mother. Such an example is the subject of this report:

Family Record. In the family observed by the author for the past 3 years, there were 7 boys and 1 girl. The girl and 1 of the boys were normal; the other 6 boys suffered repeated hemorrhages following slight trauma. The bleeding on most occasions continued until they became practically exsanguinated and then stopped spontaneously. All have had hemarthroses of the knee joints following slight trauma. They appeared as normal children in periods between attacks. In all, the tendency to bleed appeared shortly after birth and has gradually lessened as they became older. Two of the boys affected died in infancy, 1 was killed in an accident and the other died of rheumatic heart disease. Blood studies were done on the youngest and oldest. The other children were not available.

The oldest son, aged 22, when seen 3 years ago, was bleeding from the the urethra following violent exertion. The bleeding finally stopped spontaneously. He was again seen, in 1932, and came to the hospital* with a large cut on one of his fingers which seeped constantly. With a tourniquet in place, the wound was closed and a thick layer of collodion applied. These measures sufficed to stop the hemorrhage. During this visit a blood study was done. His coagulation time was increased (½ to 1 hour), the clot retracting normally. The bleeding time was normal (Duke); platelets were normal (200,000+ per c.mm.)

The youngest brother, aged 4 years, was in the hospital,† in 1931, at which time, a large abscess was opened over the right inferior margin of the mandible. Transfusions were necessary both before and after the operation. Blood studies then, and on many subsequent occasions, showed his coagulation time to be markedly prolonged (1 to 24 hours), the clot retracting. The bleeding time (Duke) was normal. The platelets

* Outdoor Department, St. Luke's Hospital, Montreal.

† Homœopathic Hospital, Montreal, Service of Dr. J. T. Novinger.

were consistently above 250,000. Despite the fact that the other brothers could not be examined, it is highly improbable that they suffered from any form of hemorrhagic diathesis such as essential thrombocytopenia, for that disease is not clearly familial.

The family history was taken from several members on separate occasions and their stories checked perfectly so that it is fairly dependable. The father's family history is irrelevant. The mother's family was known in its entirety through the 4th generation and, in addition, 2 members of the 5th. It was possible to get the names and a short history of each member of the family (see chart), since the family had resided in the same rural community for 5 generations. There was not the least tendency to bleed in any of the individuals shown in white on the chart. Most of them lived to advanced old age. There were potential bleeders (unaffected

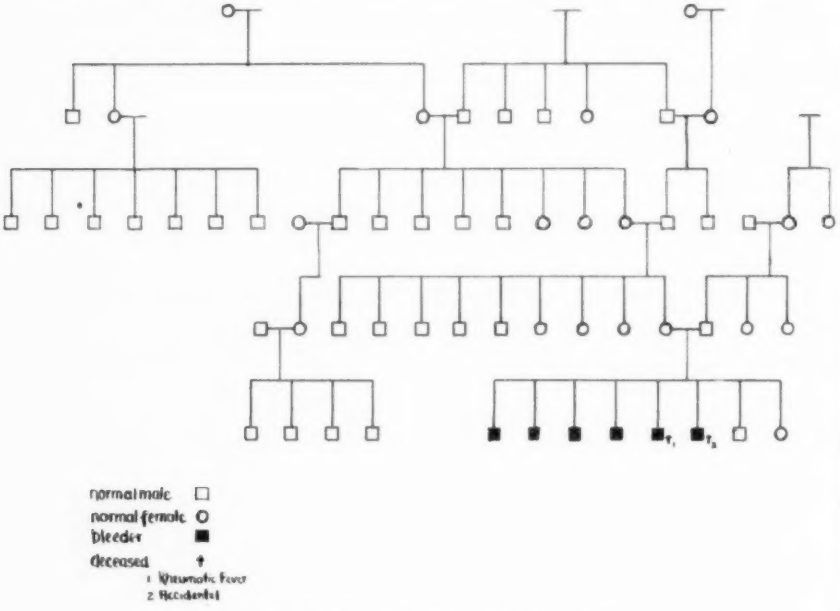

CHART I.—Family tree of hemophilic brothers.

males) in each stem of the family, if their respective mothers were carriers. The only female who was in the direct line of descent and did not have at least 5 sons was the great-great-grandmother of the patients, who had only 1 son. If we assume that the disease in this case did follow the Mendelian line of descent, then this woman must either have been a carrier or her husband was a bleeder. The history of the latter was not available. An incidental finding was that the grandparents of the patients were first cousins, but this could not alter the hereditary process in this disease.

It is barely possible that if this family and the other cases which have been reported could be traced to antiquity, an antecedent bleeder might be found. The occurrence, however, of such a large number of unaffected males would be truly remarkable, since theoretically 50% of the males in the direct female line should have

received the hereditary characters which make up the hemophilic constitution. In fact, the number is here so great that one would hesitate to attribute it to an extraordinary run of negatives under the laws of chance. We are inclined, therefore, to dismiss the possibility of hemophilia being concealed in this family for several generations and look for an explanation in one of the other two possibilities, namely, true spontaneous origin or illegitimacy. Between these it is impossible to draw positive conclusions. There seems to be no doubt that, with so many members of the family afflicted, we must look to the mother for our explanation. Either she is an example of the disease arising spontaneously in the female or she is illegitimate. Unfortunately, both of her parents are dead, so the possibility of investigating this point by the inheritance of the blood groups could not be undertaken.

Conclusions. An example of apparent spontaneous hemophilia in 6 brothers is reported. The large family tree on the mother's side practically precludes the possibility of concealed inheritance.

The author wishes to express his obligations to Prof. T. R. Waugh, in charge of the Department of Hematology in the McGill Pathological Institute, for the opportunity to study these cases, and for his many valuable suggestions.

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A FAMILIAL HEMORRHAGIC CONDITION SIMULATING HEMOPHILIA AND PURPURA HEMORRHAGICA.

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Recent literature has described certain hemorrhagic diatheses which cannot be classified with recognized types of such disorders. Glanzmann[1] described one such entity under the name "hereditary

hemorrhagic thrombasthenia." Eight families were afflicted with severe epistaxis and ecchymoses. Both sexes were involved and transmission was usually by the females. Blood studies were normal except for an occasional slightly prolonged bleeding time with an associated delay in clot retraction. Minot[2] reported 5 cases of this kind associated with an intermittent prolongation of the bleeding time. The symptoms were multiple ecchymoses and recurrent epistaxis. Cases somewhat similar have been reported by Buckman,[3] Rothman and Nixon,[4] and others.[5,6,7,8] Little has been learned about the pathogenesis.

This communication presents an heretofore unrecorded family of similar "bleeders." These conditions are to be differentiated from hemophilia and purpura hemorrhagica (thrombopenic purpura, Table 1).

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF HEREDITARY HEMORRHAGIC CONDITIONS.

	Sex involved.	Transmission through.	Site of bleeding.	Coagulation time.	Bleeding time.	Tourniquet test.	Clot retraction.	Platelet count.	Platelet resistance.
Hemophilia	Male	Female	Joints, skin and mucous membranes	Prolonged	Normal	Negative	Normal	Normal or increased	Increased
Thrombopenic purpura (purpura hemorrhagica)	Male and female	Male and female	Skin and mucous membranes	Normal	Prolonged	Positive	Delayed	Diminished markedly	Normal
Thrombasthenic purpura	Male and female	Female usually	Skin and mucous membranes	Normal	Prolonged	Positive	Delayed	Normal	Decreased
Hereditary telangiectasia	Male and female	Male and female	Mucous membranes and skin	Normal	Normal	Negative	Normal	Normal	Normal
Reported condition	Male and female	Male and female	Skin and mucous membranes	Normal	Intermittently prolonged	Negative	Occasionally slightly delayed	Normal	Normal

Results of Present Study. This condition has affected at least 14 males and 11 females during 5 generations, comprising more than 100 members. The genealogic tree of the family (Chart I) shows the occurrence of the bleeding tendency in the successive generations. The males have been more markedly affected, and have often been considered hemophiliacs. Their bleeding experiences have been varied, including those following operations such as tonsillectomies, tooth extractions and circumcision, and those associated with slight trauma. Other manifestations have included epistaxis and numerous ecchymoses or purpuric spots, both spontaneous and traumatic, in some instances covering large areas of the body. The females have characteristically suffered with menorrhagia, multiple traumatic ecchymoses and in some cases epistaxis.

The disturbance is usually observed at about puberty in the females and somewhat earlier in the males. It is generally more

severe when the individual is younger and seems to lessen in severity as age increases. The affliction, however, varies in degree of severity, some members being involved much less than others. Many

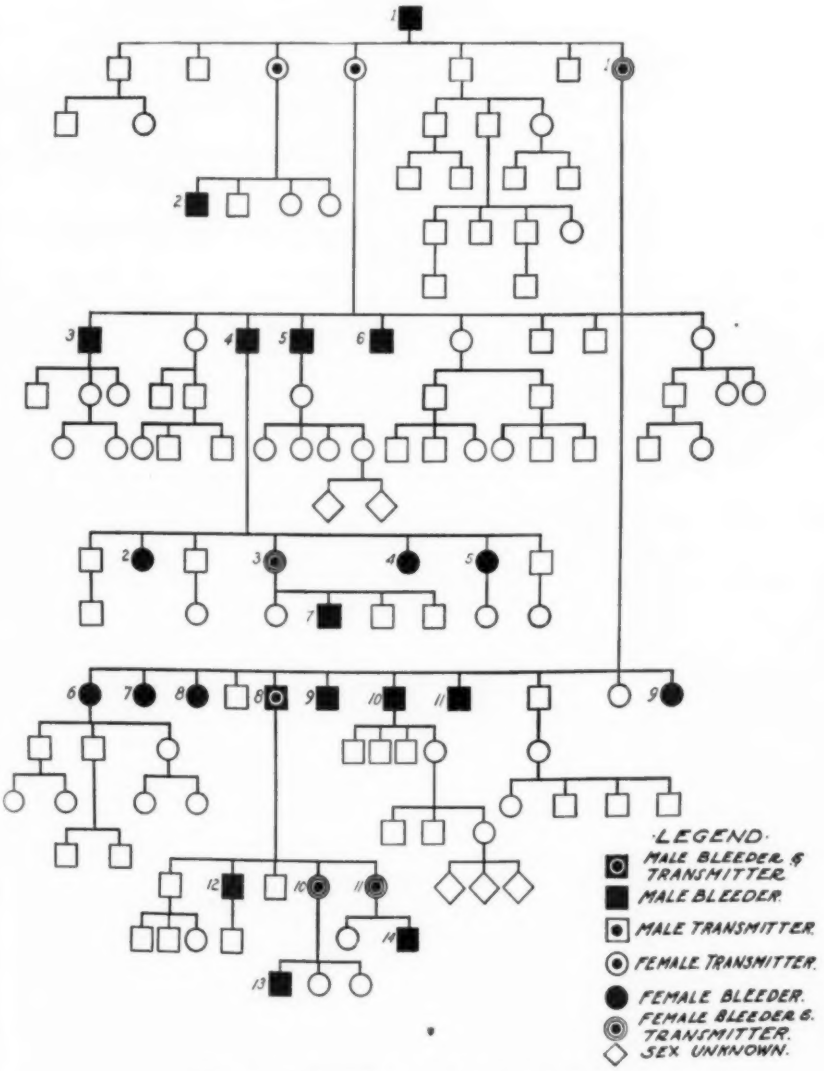

CHART 1.—Genealogic tree of reported family.

of the males have suffered hemorrhages until almost exsanguinated, while at other times the bleeding has been moderate. Death due directly to the bleeding can be ascribed in only 4 cases. "High

blood pressure" is known to "run in the family" and cerebral vascular accidents have been a common cause of death in several of the "bleeders."

Both males and females are transmitters. The female apparently transmits the more severe form of this disorder, directly to her sons from her father. This form of transmission is compatible with the genetics of hemophilia but in hemophilia the female is not involved. However, in the condition described here, the mothers of male "bleeders" exhibit the purpura to a great extent. Furthermore, males never transmit hemophilia, and in more than three score of severe bleeding experiences, no male ever developed a hemarthrosis.

As regards laboratory examination, no affected individual in our study has had a prolonged clotting time (method of Lee and White). The bleeding time (method of Duke) has occasionally been slightly prolonged, between bleeding phases. At this time the platelets are somewhat lower than normal and clot retraction is slightly delayed. Following a bleeding phase the blood picture shows an anemia and a normal leukocyte count. Sedimentation rate and blood chemistry are normal. The tourniquet and flicking tests are negative. (Controls in all the above tests included normal individuals and 1 known true hemophiliac.)

Case Abstracts. The following is a more detailed description of the affected individuals.

M (*male bleeder*) *1*, lived in Alsace-Lorraine. He suffered from uncontrollable bleedings from any site of injury on the body, had epistaxis, numerous ecchymoses and a fatal traumatic epistaxis. *M 2*, *M 5*, *M 10*, and *M 11* had numerous severe bleeding episodes, throughout life, from all parts of the body, usually following trauma and tooth extraction. Epistaxis and ecchymoses were common. *M 10* and *M 11* are said to have died from brain hemorrhage when about 50 years of age. *M 3* was admitted to the Buffalo City Hospital on November 6, 1923, bleeding from the gums. This condition had continued unabatedly for 15 days following extraction of 8 teeth and the patient was *in extremis*. Physical examination was otherwise negative except for the marked anemia. The spleen was not palpable. The blood showed a hemoglobin of 45%, red cell count 2,500,000 per c.mm.; the clotting time was 7 minutes. Blood urea was normal; urine, Wassermann test and gastric analysis were negative; the stool showed a 3+ occult blood. History revealed that the patient had throughout his life suffered hemorrhages, ecchymoses and epistaxis following even trivial trauma. The patient recovered from this experience but died 5 years later from "apoplexy."

M 4 was seldom free of ecchymoses. He had prolonged bleeding following "cuts," and epistaxis, on one occasion lasting 18 hours. Death occurred suddenly from a "stroke."

M 6, at the age of 22 months, bit his tongue and bled to death in spite of surgical intervention. *M 7*, aged 17, was admitted to the Buffalo City Hospital on September 21, 1932, with a large subperiosteal hematoma of the left leg, traumatic in origin. In the past the patient had bled profusely following circumcision at the age of 5 (a transfusion was required to check the hemorrhage); following tonsillectomy, tooth extractions and trauma, and has also had numerous ecchymoses. Physical examination showed a well developed and nourished youth with no abnormalities except for the

hematoma. The spleen was not palpable. The blood count showed a slight secondary anemia with a normal white cell and differential count. The bleeding time was 8 minutes; clotting time 8 minutes. The urine, Wassermann test and Roentgen ray plates of the left leg and ankle were negative. Temperature, pulse and respirations during 25 days' stay in the hospital were normal. On two occasions during the past year the patient had prolonged bleeding from cut fingers and recently developed an extensive ecchymosis of the eyelids and forehead following a slight injury. Repeated bleeding and clotting times, however, were normal. The platelet count on one occasion was 164,000 and clot retractility at this time was perhaps slightly delayed. A blood count on January 4, 1934, showed a normal hemoglobin, red and white cell count with a relative lymphocytosis. The patient's diet has apparently always been well balanced and includes an ample supply of meat, milk, fruits and vegetables. Skin tests with powdered group extracts of meat, fowl and fish were negative.

M 8, aged 47, an office clerk, was admitted to the Buffalo Deaconess Hospital in 1921, in a state of collapse, with a diagnosis of internal hemorrhage and died 18 hours later. Roentgen ray revealed dense fluid shadow in left pleural cavity. At *autopsy* the patient's abdomen was said to have been found filled with fresh blood, but no autopsy record is now available. The patient was considered a "bad hemophiliac." His life had been marked by many hemorrhages, both spontaneous and traumatic. Shaving was invariably followed by actual "streams of blood." "Black and blue spots" were constantly present and, on several occasions, extensive suggillations occurred, covering large areas of the body. Oozing of blood from various parts of the body frequently occurred. On one occasion the patient began oozing from the feet. This continued for several days. The patient's diet was apparently well balanced and bleeding episodes occurred throughout the year. Unfortunately, no laboratory studies are available.

M 9, aged 21, died from a traumatic epistaxis. His bleeding episodes corresponded to those of his brothers, *M 10* and *M 11*.

M 12, aged 33, the son of *M 8*, since the age of 5 has had numerous periods of prolonged bleeding from cut fingers, epistaxis, and from tooth extractions. Shaving has always been attended by bleeding and oozing in appreciable amounts. The patient's diet has apparently been well balanced and bleedings occur throughout the year. The bleeding condition, however, has of late become less severe which, the patient notes, is "ever since I stopped having boils." Physical examination on November 27, 1933, revealed a large, well built man, and no abnormal findings were demonstrable. Blood count showed a normal hemoglobin, red and white cell counts with a relative lymphocytosis. Platelet count was 350,000; the clotting time 7 minutes (control 7 minutes); bleeding time 4 minutes; clot retractility normal; prothrombin time (method of Howell) 12 minutes; the Wassermann and Kahn tests were negative. The blood calcium and phosphorus were normal in amount; the sedimentation rate was normal and the tourniquet test was negative.

M 13, aged 6, grandson of *M 8*, was admitted to the Buffalo City Hospital (service of Dr. F. J. Gustina) on November 4, 1933. The patient had been bleeding and oozing from the gums for 10 days following tooth extraction, and on the day of admission had suffered a traumatic hematoma of the forehead. Past history revealed a series of hemorrhages and ecchymoses which began at the age of 2. The patient's diet has always been well balanced. Bleeding episodes have occurred at all seasons of the year. The patient generally was in a healthy state at the time of bleeding. Physical examination showed a well developed and nourished, rather pale appearing boy of 6. He displayed a soft subcutaneous hematoma the size of a horse chestnut in the middle of the forehead, and oozing from the

gums. No telangiectasia could be found. The spleen was not palpable. After a short stay in the hospital the patient was much improved. Laboratory studies were as follows: Blood count on November 6, 1933: Hemoglobin, 68% Sahli; red cell count, 3,420,000; white cell count, 7750; the differential count showed a slight shift to the left; blood platelets, 160,000; the bleeding time, 6 minutes; clotting time, 3 minutes (capillary pipet method); the sedimentation rate, normal. Blood count on November 16, 1933: Hemoglobin, 70% Sahli; red cell count, 4,270,000; white cell count, 6900; the differential count showed a moderate increase in lymphocytes; platelet count, 230,000; clotting time, 7 minutes; prothrombin time, 12 minutes (control, 12 minutes); bleeding time, 3 minutes; clot retraction complete in 24 hours. The blood calcium, phosphorus, sugar, urea, cholesterol, chlorids and carbon dioxid combining power were normal; the tourniquet and flicking tests were negative; the urine and Wassermann tests were negative. A high-protein diet was instituted and greater care taken to avoid trauma. Subsequent studies have shown a consistently normal bleeding and clotting time, platelet count and clot retractility. During this time the ecchymoses have become fewer.

M 14, aged 6, grandson of *M 8*, has had many bleeding experiences since infancy; one of these, following circumcision, required transfusion.

F (*female bleeder*) *1*, *F 2*, *F 3*, *F 4*, *F 6*, *F 7*, *F 8* and *F 9* throughout their lives suffered from menorrhagia and ecchymoses. *F 3* has a menstrual fraction of 14(5–7)/26. Physical examination on February 20, 1934, revealed no abnormalities. Bleeding time, clotting time and clot retractility were normal; the tourniquet and Wassermann tests were negative.

F 5 had ecchymoses, menorrhagia and frequent epistaxis.

F 10, aged 31, mother of *M 13*, has bruised easily as far back as she can remember. Since puberty she has suffered from menorrhagia. Her menstrual fraction is 11(7–10)/21–28. Physical examination was essentially negative, the spleen was not palpable and no telangiectasia was demonstrable in the nose, on the gums or on the skin. Laboratory studies include: the blood on March 8, 1934, showed a normal hemoglobin, red, white and differential count; platelets, 150,000 (method of Wright); bleeding time, 4 minutes; clot retraction normal; clotting time, 7 minutes (Lee and White); the tourniquet and flicking tests negative; platelet count (March 29) was 202,000.

F 11, aged 29, mother of *M 14*, suffers epistaxis, menorrhagia and ecchymoses. These appear more severe since she has lived in the South (Florida).

Discussion of Findings in Present Series. Here, then, is a family, Germanic in origin, tainted with a hemorrhagic state. Of the 131 individuals, 71 are males, 55 are females and the sex is unknown in the remaining 5. Fourteen (20%) of the 71 males have lived or are living a life frequently interrupted by bleeding episodes; these were directly the cause of death in 4 cases. The source of the bleeding has been diverse, the skin and mucous membranes being chiefly involved. Eleven (20%) of the 55 females have manifested the hemorrhagic taint chiefly by excessive bleeding from the uterus and under the skin. This has been of serious import in only 1 case, whereas in the remainder it has been merely temporarily disabling. On the whole the females are far less severely afflicted than the males, although the occurrence of the disease is roughly the same in both sexes. No telangiectasia has been found and splenomegaly is absent. There is no definite seasonal incidence

of the bleeding episodes. All the male members of the family have been occupied by work of either a clerical or farming nature; the females have been principally housewives. There has been no undue exposure to unhygienic conditions. Trauma has been the principal factor in precipitating the hemorrhagic event, while infection has been associated in only a few cases. The diet has apparently been ample and well balanced in meats, fruits, vegetables and carbohydrates. There are no food idiosyncrasies in the family. Laboratory studies have only served to rule out the common and recognized forms of hemorrhagic states as the diagnosis in this case. Clinically there is prolonged bleeding and this brings the patient to the physician. Unfortunately examination of the patient is usually at a lesser or greater period of time after the bleeding event.

The frequent occurrence of hypertension and brain hemorrhage in the successive generations is worthy of note. At least 15 unaffected members of the family have been patients at the Buffalo City Hospital for various ailments. None of these exhibits to any degree the tendency to the pathologic hemorrhage of their relations.

Twelve of the affected males are grandsons of "bleeders," the transmission being by the female. Four of the 6 mothers of these 12 "bleeders" suffer from the purpuric condition; data on the remaining 2 are unavailable. In only one instance an affected male (*M 12*) is the son of a male "bleeder." Six of the affected females are sisters of male "bleeders" and Pratt[9] notes that sisters of hemophiliacs often suffer with purpura. The genealogic tree in regard to the males, with the exception of *M 12*, resembles that of hemophilia. Wyllie and Ellis[10] state that isolated features of purpura occur in certain hemophiliacs and *vice versa*. However, the familial affliction is chiefly purpuric in nature, and because of the similarities to the two apparently distinct hemorrhagic disorders, *i. e.*, hemophilia and purpura hemorrhagica, no diagnosis can be made with certainty in these cases. Perhaps this is in keeping with the idea advanced by Aschoff and others[11] that the name applied to the hemorrhagic diathesis is of secondary importance, for the underlying defect, which is all-important, probably lies in the reticuloendothelial system. Furthermore, evidence suggests that this defect may, in instances, be genotypic, *i. e.*, carried in the germplasm.

Conclusions and Summary. This study presents a family of more than 100 members during 5 generations, of which 25 members suffer atypical pathologic hemorrhage. Fourteen (56%) of the 25 are males; 11 (44%) are females.

The family tree in regard to the males has striking similarity to that of hemophilia, but the affliction is essentially purpuric in nature. The males have been more markedly involved, 4 of their number dying directly from hemorrhage.

The hemorrhagic incidents are variable, but consist chiefly of

prolonged frank bleeding from a cut or wound, ecchymoses and epistaxis in the males and menorrhagia and ecchymoses in the females. The coagulation time of the blood is normal; bleeding time is intermittently prolonged; platelets are numerically adequate and the clot retracts normally. Blood chemistry is normal.

There seems to be no definite relation of the bleeding to season, diet, infection or occupation.

Telangiectasia and splenomegaly are uniformly absent.

Hypertension "runs in the family;" brain hemorrhages are frequent.

No diagnosis is attempted; further studies are in progress.

NOTE.—The author is indebted to Dr. E. B. Hanan, Director of Laboratories at the Buffalo City Hospital, for his advice and encouragement during the study, and to Dr. F. J. Gustina, Chief Pediatrician, for permission to publish cases from the Pediatric Service.

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ELONGATION OF THE RED BLOOD CELLS IN A JEWISH FAMILY.

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THE human red blood cells are so consistently round that any constant deviation from their normal shape excites interest. Irregular variation in shape occurs in several types of anemia, but this is apparently of different significance from the consistently abnormal appearance of the red blood cells seen in sickle-cell anemia and in the associated states of "sicklemia" without anemia and "ovalocytosis." The occurrence of sickle-shaped erythrocytes in the blood

has for so long been associated with the negro race that the possibility of its appearance in the white race is still not generally known. The finding, therefore, of large numbers of oval, elongated and even sickled red blood cells in several members of a Jewish family in whom there was apparently no admixture of negro blood seemed of sufficient interest to warrant this report.

Various observations were made regarding the mechanism of the ovalocytosis, during the course of which the experiments of several investigators were repeated. A critical review of the literature bearing on the occurrence of elongated red blood cells, particularly in the white race, was made.

Case Abstract. Esther L., a single, white Jewess, aged 30, entered this hospital for the removal of a painless lump in the breast. She was born in Chelsea, Mass., and had always lived there or in the nearby city of Somerville. She had never been ill. On examination, she was found to be in excellent physical condition. In the upper outer quadrant of the left breast was a hard, painless, non-tender, nodular mass with an accompanying enlarged lymph node in the left axilla. Roentgen ray of the long bones and the chest failed to reveal any metastases. A radical resection of the left breast was performed. Pathologic report showed chronic cystic mastitis with carcinoma simplex and axillary metastases. Thirteen days after operation, a Thiersch graft was made following which the patient had an uneventful convalescence.

During the course of a red blood cell count a large number of elliptic and oat-shaped red blood cells was noted. Certain investigations were thereupon carried out, which are described below.

Results of Investigations. 1. Family. The patient was one of 4 children born of Russian-Jewish parents (Western Russia), who had emigrated to Massachusetts in 1890. Due to lack of coöperation, detailed information concerning the family tree was not obtained. It seemed highly improbable, however, that any admixture of negro blood had occcurred in this typical Jewish family. The father died in an accident about 20 years previously; no information regarding his consanguinity could be obtained. The mother, Anna, aged 62, had gray hair, blue eyes and a light complexion. She had been known to have mild diabetes mellitus for several years. A sister, Beatrice, aged 28, was tall and thin, had blue eyes and light-brown hair. She complained of being "highstrung" and had suffered from anorexia and fatigue for many years. She did not allow physical examination but appeared rather sallow and very nervous. A brother, Irving, aged 38, had always been well and seemed so on inspection; he also refused examination. Another brother lived in Joliet, Ill. Attempts to communicate with him were unsuccessful. The patient, Esther, had blue eyes, light-brown hair which was perfectly straight, a straight nose and thin lips. None of the members of the family possessed any negroid characteristics.

2. Routine Laboratory Studies (Table 1). Except for the abnormality of the red blood cells described below, routine labora-

tory studies failed to reveal anything of note. It is interesting that all of the members of the family studied belonged to Group II (Moss). The mother showed slight elevation of the blood sugar level.

TABLE 1.—BLOOD STUDIES IN 4 MEMBERS OF A FAMILY.

	Esther (patient).	Anna (mother).	Beatrice (sister).	Irving (brother).
Hemoglobin	90	90	87	92
Red blood cells, millions	5.2	4.65	4.32	4.75
White blood cells	14,400	6400	10,800	6900
Platelets	812,000			
Reticulocytes, %	2.3			
Blood group (Moss)	II	II	II	II
Fragility of red cells	0.44-0.34	..	..	0.46-0.36
Sedimentation rate, mm. per min.	1.05			
Mean corpuscular volume	78			
Blood sugar	75	185	..	74
Non-protein nitrogen	30			
Icterus index	5	..	..	7.5
Quantitative bilirubin, mg. per 100 cc.	0.3	..	..	0.5

3. STUDIES OF THE RED BLOOD CELLS. A. *Morphology.* The red blood cells varied markedly in their morphologic appearance. This was particularly true in the cases of Esther and Beatrice. The mother's red blood cells showed but little deviation from the normal round shape; the brother's cells showed moderate elongation.

The red blood cells could be arbitrarily divided into the following groups: round, oval, elongated and sickled. The round cells had the same diameter throughout. The oval cells presented one diameter definitely longer than the other; in measurement they varied from 6 by 8 micra to 4 by 9.5 micra. The elongated cells usually appeared as cigar-shaped forms, measuring 2 by 10 micra in size. The so-called "oat cells" of certain authors were included in this category. These presented long pointed ends from which extended a long filament. The sickle-shaped cells were characterized by their definitely curved banana or sickle-shaped appearance. The amount of curvature of the cell varied from an arc of 10 degrees to one of 170 degrees.

TABLE 2.—TYPES OF RED BLOOD CELLS IN THE SUBJECTS STUDIED.

	Round, %	Oval, %	Elongated, %	Sickled, %
Esther:				
0 hr.	41	32	20	7
24 hrs.	15	45	39	1
Beatrice:				
0 hr.	8	62	26	4
24 hrs.	5	64	30	1
Irving:				
0 hr.	35	53	9	0
24 hrs.	20	71	9	0
Anna:				
0 hr.	98	1.5	0.5	0
24 hrs.	96	2.0	2.0	0

The abnormalities in shape of the red blood cells could be best observed in fresh, unfixed preparations of blood spread under a thin coverslip rimmed with vaselin, and in supravital preparations stained with Dameshek's platelet-reticulocyte solution.[1]

B. *Quantitative Aspects.* 1. *The Effect of Time Upon the Sickling Phenomenon.* The percentage of abnormally shaped red blood cells when blood was first drawn varied in each subject from day to day. In the case of Esther, the cells in which one diameter was longer than the other varied from 3% to 62%; in Beatrice, they were higher, from 80% to 92%; in Irving, from 48% to 62%; and in Anna, the mother, from 0% to 2%. Since the mother at no time showed any sickle-shaped cells, it is probable that her red blood cells were within normal morphologic limits.

Despite the variation in the number of abnormally shaped red blood cells from day to day in the freshly drawn preparations, it was striking to note that the end results of allowing the preparations to remain at room temperature for 24 to 28 hours were always approximately the same (Table 3). The greatest incidence in abnormal forms occurred at 48 hours, although there was but little difference in the number of these forms at 24 and 48 hours. After 48 hours and usually after 72 hours, the cells began to assume a rounded appearance, and after a week at room temperature, only an occasional oval or elongated cell was seen (Table 4).

TABLE 3.—VARIATION IN PERCENTAGES OF DIFFERENT TYPES OF RED BLOOD CELLS IN SUBJECT, ESTHER, ON DIFFERENT DAYS.

	Round, %	Oval, %	Elongated, %	Sickled, %
May 3:				
0 hr.	52	28	14	6
24 hrs.	15	46	32	7
June 15:				
0 hr.	34	45	20	1
24 hrs.	15	45	39	1
June 26:				
0 hr.	39	30	25	6
24 hrs.	18	42	41	9

TABLE 4.—EFFECT OF TIME OF STANDING ON SHAPE OF RED BLOOD CELLS IN SUBJECT, ESTHER.

Hours.	Round, %	Oval, %	Elongated, %	Sickled, %
0	97	3	0	0
2	84	12	4	0
20	4	59	35	2
24	0	45	45	10
30	0	22	63	15
45	0	2	78	20
72	8	20	54	18
120	30	45	21	4
144	70	12	17	1

2. *The Effect of Temperature.* The temperature at which the preparation was kept affected somewhat the rate of anisocytosis, and possibly its degree. Thus, when a preparation of fresh blood was placed in a refrigerator, elongation of the red blood cells became definitely diminished and fewer red blood cells were abnormal at the end of 24 hours. At incubator temperature (37.5° C.) there appeared to be a slight increase in the rate of anisocytosis as compared to that at room temperature (24° C.) (Table 5).

TABLE 5.—EFFECT OF TEMPERATURE ON THE MORPHOLOGY OF THE RED BLOOD CELLS.

	5° C.			21° C.			37.5° C.		
	Round, %	Oval, %	Elongated, %	Round, %	Oval, %	Elongated, %	Round, %	Oval, %	Elongated, %
0 hr.	33	29	28	33	38	29	45	35	20
18 hrs.	31	38	31	18	40	42	4	46	50
24 hrs.	74	18	8	20	36	44	12	40	48

3. *The Effect of Mechanical Factors.* Abnormally shaped cells were found in various parts of all preparations. This was particularly noted because of the statements made by various authors (see Discussion) that sickling occurred most commonly in the center of a preparation, *i. e.*, farthest away from the source of oxygen supply. The effect of *pressure* upon the development of deformity of the red blood cells has been commented upon by various observers. The abnormally shaped red cells appeared to be definitely more plastic than the round cells. Pressure upon certain sections of the preparation which contained many round cells caused a definite increase in the rapidity of appearance of the elongated cells. However, the end result after 24 hours was the same whether or not compression had been used. Pressure upon oval and elongated cells frequently brought about the appearance of various bizarre forms, which retained their shape for 2 to 10 minutes. It seemed probable that pressure caused the development of elongation somewhat more rapidly in those cells which already possessed the latent tendency to become elongated.

4. *The Effect of Roentgen Rays.* This was observed by two methods: (1) Fresh preparations of blood were exposed (*a*) immediately for 2 hours and (*b*) after standing at room temperature to deeply penetrating Roentgen rays; and (2) preparations of blood were obtained at regular intervals from the patient while she was receiving deep Roentgen ray therapy of the axilla by the Coutard method. No definite effect on the rate or extent of elongation of the red blood cells was noted (Table 6).

5. *The Effect of Various Substances.* (*a*) *Anticoagulants.* Fresh wet preparations made from blood mixed with heparin, sodium oxalate and Hayem's solution developed about the same degree of deformity on standing at room temperature as did fresh preparations made without the use of an anticoagulant (Table 7).

(*b*) *Various Concentrations of Salt Solution.* "Fragility tests" were performed with various concentrations of sodium chlorid in two subjects, Esther and Irving. With Esther the red cells began to hemolyze at 0.42%, hemolysis becoming complete at 0.34%. With Irving, the figures were 0.44% to 0.36%. The number of oval and elongated cells in the most dilute salt solutions was

definitely diminished (Table 8), indicating that the abnormally shaped red cells were slightly more fragile. "Shadows" of the elongated red blood cells could be observed in the partially and completely hemolyzed preparations suggesting that these cells, as well as the more normal round ones, had a definite structure or stroma not dependent upon such transient factors as external pressure or anoxemia.

TABLE 6.—EFFECT OF EXPOSURE (*a*) OF RED BLOOD CELLS TO ROENTGEN RAYS, (*b*) OF THE PATIENT TO ROENTGEN RADIATION UPON THE CELLULAR MORPHOLOGY.

(*a*) *Fresh Preparations Exposed to Roentgen Rays.*

Time of exposure.	0 hr.		4 hrs. after exposure.		24 hrs. after exposure.	
	Oval, %	Elongated, %	Oval, %	Elongated, %	Oval, %	Elongated, %
0	38	24	39	32	44	41
30 min.	29	36	34	40	38	44
60 min.	34	28	38	31	44	39
90 min.	38	18	41	24	36	46
120 min.	21	29	26	34	34	43

(*b*) *Patient Given Roentgen Ray Therapy.*

Length of time of Roentgen ray therapy (Coutard method).	Fresh.		4 hrs.		24 hrs.	
	Oval, %	Elongated, %	Oval, %	Elongated, %	Oval, %	Elongated, %
6/12 0	54	16	58	22	58	29
6/15 1 hr.	45	20	47	24	51	32
6/16 1½ hrs.	30	15	36	22	30	20
6/26 6 hrs.	30	25	33	38	42	41
7/6 7½ hrs.	56	28	54	32	61	29

TABLE 7.—EFFECT OF ANTICOAGULANTS ON THE PERCENTAGES OF ABNORMALLY SHAPED RED BLOOD CELLS.

	Fresh.			Heparin.			Sodium oxalate.			Hayem's solution.		
	Oval, %	Elongated, %	Sickled, %	Oval, %	Elongated, %	Sickled, %	Oval, %	Elongated, %	Sickled, %	Oval, %	Elongated, %	Sickled, %
0 hr.	28	31	1	20	38	0	36	35	1	42	33	1
24 hrs.	44	44	4	36	48	1	40	47	3	49	32	1

TABLE 8.—EFFECT OF OSMOTIC TENSION ON OVAL CELLS.

% NaCl.	Esther.		Irving.	
	Oval, %	Elongated, %	Oval, %	Elongated, %
0.46	16	4	42	16
0.44	20	12	32	5
0.42	22	16	43	10
0.40	26	11	40	10
0.38	32	4	24	1
0.36	26	6	Hemolyzed	

(*c*) *Various Chemicals.* Traces of potassium cyanid in heparinized blood produced a rapid increase in the development of oval

cells, so that within 7 minutes 80% to 90% of the red blood cells were oval in shape. However, after 25 minutes, the red cells appeared to develop a thick membrane and to lose their pliability. Marked elongation of the red blood cells did not occur in these preparations.

A drop of a 10% aqueous solution of *picric acid* added to 2 cc. of heparinized blood caused some of the oval red blood cells to become rounded, although no effect on the elongated cells could be seen.

(*d*) *Effect of Certain Gases.* Hahn and Gillespie[2] concluded, after extensive investigation, that sickling of the red blood cells occurred with conditions of anoxemia. They devised a method for permitting the cells to come in contact with the gas to be tested. This method, in simplified form, was used in our investigations.

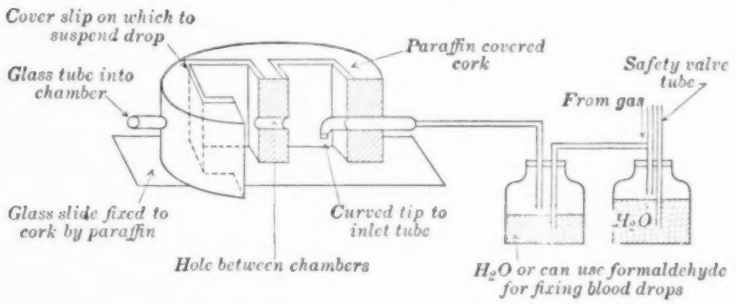
Cover slip on which to suspend drop
Paraffin covered cork
Safety valve tube
Glass tube into chamber
From gas
Glass slide fixed to cork by paraffin
Curved tip to inlet tube
H_2O
Hole between chambers
H_2O or can use formaldehyde for fixing blood drops

FIG. 1.—Schematic three-quarters cross section of gas compartments and of gauge bottles.

Method. Two "gas chambers" were constructed from a large cork (3 in. in diameter and 1 in. long) by punching 2 square holes just large enough to fit vaselin-rimmed coverslips over each. A small hole running through the diameter of the cork (Fig. 1) connected the 2 compartments. Into each compartment projected a small glass tube with a curved end. These tubes could be so adjusted by turning them that the incoming gas might play either directly on the hanging drop or into any portion of the chamber. The entire cork was thoroughly covered with a thin layer of melted paraffin and fastened by means of paraffin to a glass slide. Since the ends of the slide projected at either side of the cork, the entire apparatus could be placed on the microscope and moved about by means of the mechanical stage. Drops of blood treated with a suitable anticoagulant were placed on coverslips which were rimmed with vaselin and inverted over the 2 chambers. Examination was made with the high dry lens. The coverslips could be removed at any time for preservation. The various gases were passed into the chambers after preliminary passage through bottles partly filled with water. This procedure served not only to moisten the gases but to act as a pressure valve. Exit of the gases took place by means of an outlet tube. It was found in practice that oxalated blood prevented positive results and that if the heparinized blood was diluted slightly (25%) with Hayem's solution, rouleaux formation of the red blood cells could be prevented. Red cells from another subject could be used in 1 of the 2 compartments as a control during each experiment.

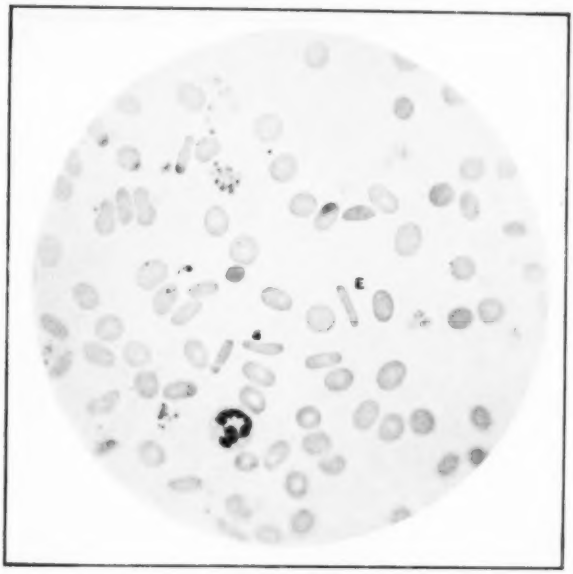

FIG. 2.—Stained blood smear of patient, Esther L. (× 800.) Note the marked variation in shape of the red blood cells with the numerous oval forms and the occasional elongated (*E*) forms. One red blood cell (*S*) shows slight sickling.

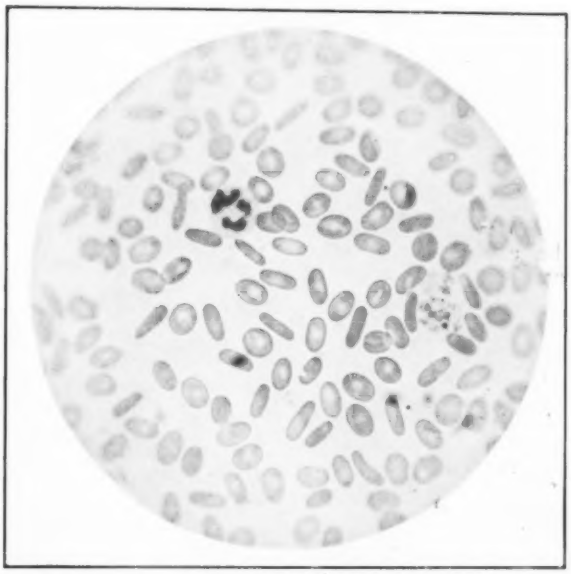

FIG. 3.—Stained blood smear of Beatrice L. (× 800.) The tendency to elongation of the red blood cells is greater than in the case of Esther.

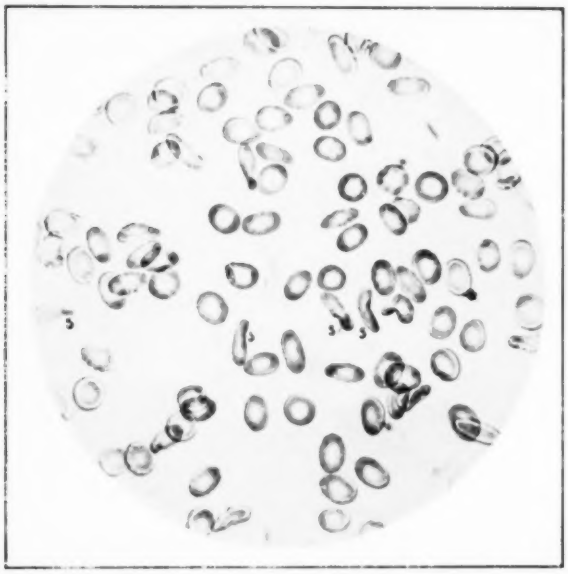

FIG. 4.—Fresh preparation of blood from patient, Esther L., after standing at room temperature for 3 hours. The cells marked *S* show a slight sickling tendency. (× 800.)

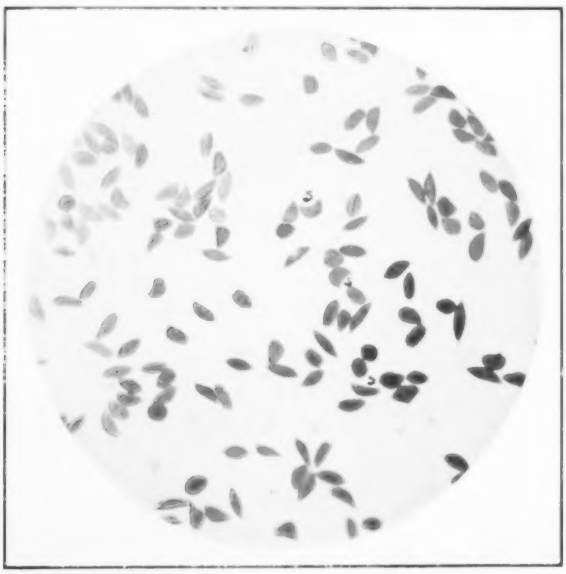

FIG. 5.—Moist preparation of blood from patient, Esther L., after standing at room temperature for 24 hours. (× 500.) Note that the great majority of the red blood cells are normally shaped and that several have assumed a "sickle" shape (*S*). Filaments projecting from the ends of certain of the cells may be noted.

1. *The Effect of Carbon Dioxid.* Carbon dioxid passed into the gas chamber for 10 minutes caused striking elongation in the great majority of the red blood cells. After 25 minutes of exposure, the cells became rounded and appeared slightly swollen.

When oxygen was passed into the chamber at the time when most of the red cells had become elongated, no reversal to the initial round or oval forms was accomplished. This observation is contrary to the experience of Hahn and Gillespie.[2]

In certain experiments the elongated forms were fixed by passage of formaldehyde gas into the chamber. (This gas was produced by passing the carbon dioxid gas through a bottle containing a warm 40% solution of formalin.) The suspended drop was then carefully and slowly dried by playing the formaldehyde gas directly into it. Slow drying was found necessary for proper fixation.

2. *The Effect of Nitrous Oxid.* Nitrous oxid caused an increase in the percentage of oval forms, although no increase in the number of elongated cells took place.

3. *The Effect of Oxygen.* The failure of oxygen to alter the shape of the elongated cells produced by carbon dioxid has already been noted. No increase in anisocytosis took place when blood was drawn from a finger made cyanotic for 15 minutes by the application of a tourniquet; subsequent oxygenation of this blood in the above-described gas chamber caused no change in their appearance. Again, no alteration in shape occurred when blood flow was stimulated by immersing the hand in warm water before the finger was pricked.

The effect of increasing the oxygen content of the blood was studied by placing the patient in an oxygen tent in which the oxygen content of the air was approximately 45%. Three hours' constant stay in this tent produced no diminution in the number of oval or elongated forms.

TABLE 9.—RELATION OF ANEMIA TO ABNORMALLY SHAPED CELLS.

Date.	Hemoglobin (Sahli), %	R.B.C., millions.		Abnormally shaped red blood cells, %		
				Oval.	Elongated.	Sickled.
5/3	90	5.20	A	28	14	6
			B	46	32	7
5/17	60	2.75	A	47	38	7
			B	32	49	4
5/24	65	2.61	A	63	12	0
			B	61	24	0
6/12	52	2.90	A	45	20	1
			B	45	39	1
6/16	64	3.10	A	30	15	0
			B	39	20	1
6/26	80	4.25	A	30	25	6
			B	42	41	9
7/16	82	4.60	A	56	28	2
			B	61	32	1

(*e*) *Effect of Anemia.* Opportunity presented itself in the patient, Esther, to study the proportion of abnormally shaped red cells not only when the erythrocyte count was normal, but when

she developed a moderate degree of anemia following operation. The greatest proportion of oval and elongated cells in freshly drawn blood was present when the red blood cell count was at its lowest level (2,610,000) (Table 9). However, about the same proportion was noted when the red blood cells later rose to 4,600,000. The tendency for marked diurnal variation in the percentage of abnormally shaped red cells has been noted above and probably accounts for the variations noted at the different levels of red cell count. Beatrice and Irving, although presenting normal hemoglobin percentages and red blood cell counts, showed a moderate to marked ovalocytosis.

(*f*) *Control Studies of the Percentage of Oval and Elongated Red Blood Cells in a Miscellaneous Group of Patients.* Blood obtained from 135 unselected clinic and hospital patients (all white) was examined for the presence of oval and elongated cells. The customary fresh wet preparations were made and examined immediately and after 24 hours. In 3 instances, 3% of the red blood cells were oval and elongated; in 4 instances, 1% of the cells; in 11 instances, 0.25% to 0.5% of the cells; in 30, 0.1% to 0.2% of the cells were oval; while in 40, 1 abnormally shaped red blood cell per 1000 counted was found. In the remainder of the 47 patients no oval or elongated cells were noted. These results indicate that the presence of an occasional oval or elongated red blood cell may be of no significance.

Discussion. 1. Review of Literature (With Special Reference to the Occurrence of Elongated Red Blood Cells in the White Race). The great majority of the cases of sickle-cell anemia and of cases showing sickled, elliptic and oval shaped red blood cells without anemia have been found to occur in the colored race. The literature has been well reviewed by Steinberg.[3] That this disorder of the red blood cells occurs in individuals of the white race is still doubted by some who have written on the subject (Musser and Wintrobe[4]). However, several well-documented observations are now on record. Bishop,[5] in 1914, described the occurrence in a white man and his sister of about 75% of oval shaped red blood cells. Four other members of this family had normal blood cells. Huck,[6a] and Huck and Bigelow,[6b] in 1923, made extensive studies of the effect of various substances upon the abnormal red blood cells found in 2 of 14 members of a white family. The 28-year-old patient and her mother each had 50% to 80% of oval red blood cells, but were otherwise in good physical condition and not anemic. Castana,[7] in 1925, reported the first case (in an Italian child) of definite anemia with the presence of sickled red blood cells in an individual of the white race. No illustrations are, however, given and no mention is made of the behavior of the red blood cells in fresh "wet" preparations. Archibald,[8] in 1926, described the occurrence of sickle-cell anemia in a 2-year-

old Arab child, a native of the African Sudan. The parents showed no sickled cells. This case, because of the definite possibility of racial admixture, should probably be excluded as a definite instance of the occurrence of sickle-cell anemia in the white race. The same holds true for Stewart's[9] report (1927) of the occurrence of sickled cells in 2 Cuban children. Both of these children had definitely negroid facial characteristics, and the mother was probably a negress. The first case from Europe was reported, in 1928, by van den Bergh,[10] who found 4 instances of elliptic red blood cells in a Dutch family. This was shortly followed by the reports of Bernhardt[11] and Günther[12] of German patients with the same disorder. Cooley and Lee,[13] in 1929, reported a definite case of sickle-cell anemia in a Greek child, and in the same year Hunter and Adams[14] observed in this country a Dutch family in which 3 generations presented elliptic red blood cells. Numerous relatives of this family were found by van den Bergh,[15] in Holland, and the derivation of the elliptic red cells was finally traced to the third of 4 wives which the great-grandfather had married in Holland. The relatives of this third wife presented several instances of abnormally shaped erythrocytes. Sights and Simon,[16] in 1931, reported a case of sickle-cell anemia in an American of Scotch-Irish parentage, and Rosenfeld and Pincus[17] made careful studies of members of 3 generations of an Italian family who presented various degrees of sickling. Lawrence[18] studied a number of patients and medical students in a university hospital and found several instances of sickling of the red blood cells. In 1931, the same author[19] found oval red blood cells in 2 patients with pulmonary tuberculosis. One of these was Jewish and is thus the first representative of his race in whom sickled or oval red blood cells have been reported. Roth and Jung[20] found oval red blood cells in a white woman, aged 30 years. Cheney[21] studied 81 members of an Italian family, 14 of whom showed oval-shaped red blood cells, and Grzegorzewski,[22] in 1933, was also able to find 14 instances of the disorders in 5 generations of a white family living in Danzig.

2. The Terms Sickle Cell, Sickle-cell Anemia, Ovalocytosis, Etc. The terminology referring to these variations in the shape of the red blood cells has become greatly confused. The name "sickle-shaped red blood cells" given by Herrick,[23] in 1910, has been retained despite such suggestions as "drepanocytosis" (Hahn[2b]) and "meniscocytosis" (Graham and McCarty[24]), etc.

"Latent sickling" (Emmel[25]), "the sickle-cell trait," "latent sicklemia" are all terms indicating changes in the morphology of the red blood cells when blood is allowed to remain in wet preparations for 24 hours. "Sicklemia" refers to the presence of numbers of sickled red blood cells found at the moment blood is obtained. When anemia is also present, the condition is known as *sickle-cell anemia* (Mason,[26] 1922). "Ovalocytosis"[11b] refers to blood in which,

although most of the red blood cells are elongated in one diameter, only an occasional one is bent in the characteristic sickle fashion.

Definite gradations in this type of abnormality of the red blood cells are thus seen to occur. These have been carefully studied by Günther[12] and Penati.[27] The slightest degree of abnormality is represented by the oval-shaped cells. When these occur in large numbers (10% of the red blood cells or greater), the term "ovalocytosis" may be used. The number of these cells in a wet preparation usually increases greatly on standing, and some of the cells become definitely elongated and frequently cigar or fusiform in shape. Elongation may thus be said to be the next degree of abnormality. The final and most marked stage, in which a banana or "sickle" shape is assumed, is called the "sickle cell." Although certain observers conclude that "ovalocytosis" and "sicklemia" are separate phenomena, it would appear unwise to differentiate sharply between them, since they may be closely related stages of the same general disturbance of the red blood cells.

3. Racial and Familial Characteristics. As noted above, most cases of oval and sickle-shaped red blood cells have been reported in the colored race. The occurrence of an instance of elongation in a white person, therefore, is always either doubted (Musser and Wintrobe[4]) or the question of racial admixture either recent or remote[17] is entertained. The possibility of recent negroid admixture in our typically Jewish family, none of whom possessed any negroid characteristics whatsoever, is exceedingly remote. However, it must be admitted that the possibility of an admixture of negro blood in the distant past resulting in the transmission of a sickle-cell trait cannot certainly be excluded. This possibility may account for the occurrence of other cases in typically "white" individuals, although it must also be admitted that the sickle-cell trait may have been present for centuries in certain pure strains of white individuals.

The familial occurrence of this disorder is well known and needs no elaboration here. The exact mode of transmission, whether by male or female, and whether by a strictly Mendelian type of inheritance, has not yet been worked out.

4. Pathogenesis of the Disorder. Race and heredity probably represent the greatest single factors in the occurrence of this disorder. There is no doubt, however, that the sickling trait may be modified *in vitro* by various mechanical and chemical factors. Hahn and Gillespie[2] emphasized the factor of anoxemia. Scriver and Waugh,[28] by altering the oxygen content of the forearm by means of a bandage, found that the degree of sickling varied directly with the decrease in oxygen tension. Sydenstricker,[29] however, found that the sickle cells in a case of sickle-cell anemia were unaffected by oxygen, and Graham and McCarty[24] failed to find an increase in the percentage of sickled red cells in blood removed from the heart under anaërobic conditions 27 hours after death.

Failure to change the shape of the red blood cells in our experiments by modifying the oxygen saturation of the blood in the circulation by either hyperoxygenation or anoxemia also serves to cast doubt upon the theory of anoxemia. Attempts to explain the elongation of the red blood cells by mechanical factors (pressure on the coverslip, etc.) have failed of proof. Auer,[30] in a recent study of the structure and function of filaments produced by living red corpuscles, concluded (on theoretical grounds) that "these filaments are probably the agents that cause cell deformity in sickle-cell anemia."

It is still not entirely certain whether the elongated red blood cells are produced as such in the bone marrow or whether their development takes place in the circulating blood. Several observers have made distinctly contradictory statements in regard to this question. Unfortunately, we were unable to study the bone marrow at biopsy in our cases. However, it was observed that the reticulocytes present were always round, and showed no tendency toward elongation of one of the diameters. This finding led to the speculation that it was only the more mature red blood cells which developed varying degrees of elongation and, therefore, that the phenomenon occurred in the circulating blood. Against this speculation, however, is the observation (questionable) by Roth and Jung[20] of oval red blood cells in the marrow.* The question as to whether the oval cells were in the marrow tissue or the circulating blood of the marrow would still remain open. Bernhardt,[11] in 1928, found that the bone marrow in a case of sickle-cell anemia had normal erythroblasts and normoblasts and concluded that the oval cells first appeared in the peripheral blood. That anemia does not of itself predispose to ovalocytosis is now definitely accepted. Conversely, the presence of large numbers of circulating ovalocytes does not predispose to anemia. Of 46 cases of ovalocytosis occurring in people of the white race, 37 were in good health and presented normal blood pictures. The others had slight degrees of hypochromic anemia probably associated with the various chronic diseases which were present.

The significance of the observations of the effect of various physical and chemical factors upon the red blood cells *in vitro* must to a certain degree be questioned. It cannot be denied that, although the red blood cells respond in various definite manners to various stimuli when studied outside the circulating blood, it is wholly improbable that striking changes either in pH, oxygen saturation, temperature, etc., occur within the body. These more or less artificial observations must be taken, therefore, as interesting

* Corrigan and Schiller,[31] in a very recent communication, note that "a number of nucleated red cells appeared sickled" in the bone marrow from a case of sickle-cell anemia.

phenomena which may well have no reference to the underlying pathogenesis of the disorder. The most that can be said at present is that certain individuals have an hereditary tendency toward elongation of their red blood cells.

Summary. Large numbers of oval, elongated and sickled red blood cells were found in 3 members of a Jewish family, in whom no admixture of Negro blood could be elicited.

Studies of the effect upon these cells of time, temperature, pressure, Roentgen ray radiation, anticoagulants, various chemicals, certain gases and anemia were made.

The literature bearing on the occurrence of elongated and sickled red blood cells in individuals of the white race is reviewed.

It is probable that oval, elongated and sickled red cells and sickle-cell anemia represent various gradations in the same general abnormality of red blood cells. The significance of certain observations made upon the red cells *in vitro* is questioned.

The most important factor in the pathogenesis of the disorder appears to be that of heredity.

The appearance of oval, elongated and sickled red blood cells in members of the white race cannot longer be questioned.

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EXPERIMENTAL INTERFERENCE WITH CONDUCTION IN THE HEART.

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In order that the problems of conduction in the heart may be solved, there must be no divorce between the facts of function and of structure. There is reason to suppose that theory has outrun observation and does not merit our full confidence, as the following citations imply.

There has been much inconsistency in the description of cardiac muscles (see Robb[1,2,3] for extensive references), a confusion which perhaps influenced Lewis'[4,5] view, that they were without conduction significance. Unfamiliarity with the demarcation between adjacent muscles led to an easy acceptance of this opinion.

The statement that heart muscle forms a syncytium is only a partial truth. Pettigrew[6] quotes unpublished work of his students confirming their observation that when the muscle layers are separated, one from another, no muscle fibers are cut, only connective tissue strands being broken. (See also Robb.[1]) Pettigrew also examined microscopic preparations to confirm the gross observation. One must then limit the statement that "the cardiac muscle forms a syncytium" to mean that *within any given muscle bundle the fibers form a syncytium.* Thus, there is not a syncytial muscular connection between any two muscle bundles, *e. g.*, the superficial and deep sinospirals. The one overlies the other in areas, but the two are ever separated by connective tissue septa in which are found the bloodvessels. Various textbooks of histology will support this statement (*e. g.*, Fig. 172, Lewis and Stöhr). The physiologic implication is that excitation would doubtless take the path of least resistance, *i. e.*, along the syncytium of a given muscle, rather than cross the connective tissue barrier from one muscle to another. Direct linear distances, disregarding muscle boundaries, were used in the calculation of conduction rates.

The blood supply to the ventricles has been admirably described by Gross,[7] and further details have been added by Wearn.[8] However, the specific blood supply to the individual muscle bundles has been uninvestigated. In such a study, presently to appear, each muscle is found to have a fairly precise blood supply (Robb). Ligation of a definite branch of the coronary system will consistently cause anemia in a specific portion of a given muscle. The fact that

one may limit an infarct to a single muscle makes the study of conduction less complicated.

Knowledge of the actual distribution of the conducting system in the heart still awaits final evaluation. The classical description recognizes a sinoauricular node (an isolated structure), the auriculoventricular node of Tawara, the bundle of His, right and left branches of the bundle and subendocardial Purkinje ramifications. The studies of Keith,[9] Kent,[10] Curran,[11] Todd,[12] Taussig,[13] and Abramson and Cardwell[14,15] all suggest the possibility of a more general distribution in mammals, including man. The Purkinje system unquestionably ramifies through the heart substance in ruminants, and perhaps in all mammals, even connecting the two ventricles; also multiple muscular connections between auricle and ventricle have been supported.

A further assumption is commonly made by physiologists, namely, that a stimulus applied to the surface of the heart has to pass through muscle tissue only. On this basis, two types of conduction were inferred—one of 400 mm./sec. for ventricular muscle, and another approximating 5000 mm./sec. for Purkinje substance. In the light of the histologic data referred to above—particularly that of Todd and Abramson, this assumption, and hence the conclusion as to two conduction rates, is open to suspicion. The apparent differences in conduction rate may be only a question of the length of the pathway actually involved.

Because these facts regarding the gross anatomy, the blood supply and the distribution of the Purkinje tissue to the ventricular muscle bundles have not been taken into sufficient account by the physiologists in the present theory of conduction in the ventricle, it seems obvious that it should not merit great confidence.

Experimental Methods. Various methods may be employed to study conduction in the ventricle. A technique hitherto untried is the elimination of muscle bundles, one at a time, by appropriate vessel ligation, and observation of resultant change in the electrocardiogram. The author[17,18] has reported elsewhere two such studies. It is also important to repeat the classical procedures of Lewis, having due regard to the anatomic facts stressed above. This paper is concerned with a repetition of two such experiments.

On dogs anesthetized with chloretone (0.25 gm./kg., 1st series) or with pentobarbital (50 mg./kg., 2d series), the thorax was opened, the heart exposed and the pericardium stitched to the edges of the wound. In the 1st series there were attached directly to the heart electrodes of glass tubes having a gelatin-saline plug in which was embedded a thick silver wire coated with silver chlorid. A small amount of absorbent cotton was inserted into the gelatin at the tip of each tube, and this cotton wick, wet with 0.9% saline, was attached to the heart by a single superficial stitch. This ensured a constant contact and yet allowed for free movement of the ventricle. Such electrodes are strictly non-polarizable and have a resistance of 500 Ohms or less. All records were taken with standard electrocardiographic technique. A total of 66 muscle studies have been made on 21 dogs.

*Series I.** One of the experiments upon which Lewis' theory of conduction in the ventricle depends is that of attaching two direct electrodes to the surface of the heart and subsequently making a cut between them. Lewis found that this procedure did not alter the conduction time from one electrode to the other.

In Fig. 1 are shown typical data obtained upon repeating this experiment. The small insert, at the left, is reproduced from Lewis,[5] and shows where his electrodes were placed. If the experiment is repeated with the electrodes in that position, Lewis' observation is confirmed. The corresponding insert (*F*) is a reproduction from Mall[19] and shows the direction of fibers on the surface of the heart. It is obvious that a cut in the position made by Lewis only separated the fibers in the syncytium. If the experiment is modified so that the electrodes are placed as in the lower insert on the right (*G*), that is, in such a position that the fibers are cut transversely, then a marked change in the electrocardiogram appears. This alteration is observed in "natural" as well as in "excited" beats. The contour of the *Q–R–S* complex is altered and the duration increased subsequent to the cut. Attention is called to the fact that not only are the contour and time relations of the direct leads altered, but similar changes are to be seen in the indirect leads. Also, one notices in tracing *A*[2] that the mere attachment of the direct electrodes to the surface of the heart has elevated the *R–T* segment and that subsequent to the cutting this segment is still further raised. (Randles, Gorham and Dresbach.[22])

Series II.† In Fig. 2 is shown a diagrammatic representation of the superficial sinospiral muscle. At the point marked "1" the muscle is of small compass. The blood supply to the internal portion (anterior papillary muscle) is derived from branches of the left anterior descending branch of the left coronary artery and can easily be identified and ligated. Rendering the internal portion of this muscle anemic causes an elevation of *R–T* in all leads (Fig. 3, *3*; also Robb[17]).

If in addition to this lesion one makes a cut transverse to the muscle fibers proximal to the ligation, in the position marked "2," no further change occurs (Fig. 3, *4*).

A branch of the left fork of the bundle of His enters this muscle near its mitral insertion. We were able to introduce an instrument through the left auricular appendage into the left ventricle, where cuts were made on the anterior papillary muscle, thus breaking its connection to the bundle of His. The same type of electrocardiogram is obtained (compare Fig. 3, *4* and *5*), the only additional change found being the complete loss of the negative *S* wave.

* These experiments were performed with the help of Dr. Easby and with equipment supplied by the Laboratory of Physiology, University of Pennsylvania and by the Philadelphia General Hospital.

† Experiments performed with the aid of Dr. J. G. Fred Hiss—some in the Laboratory of Physiology, School of Medicine, Rochester University.

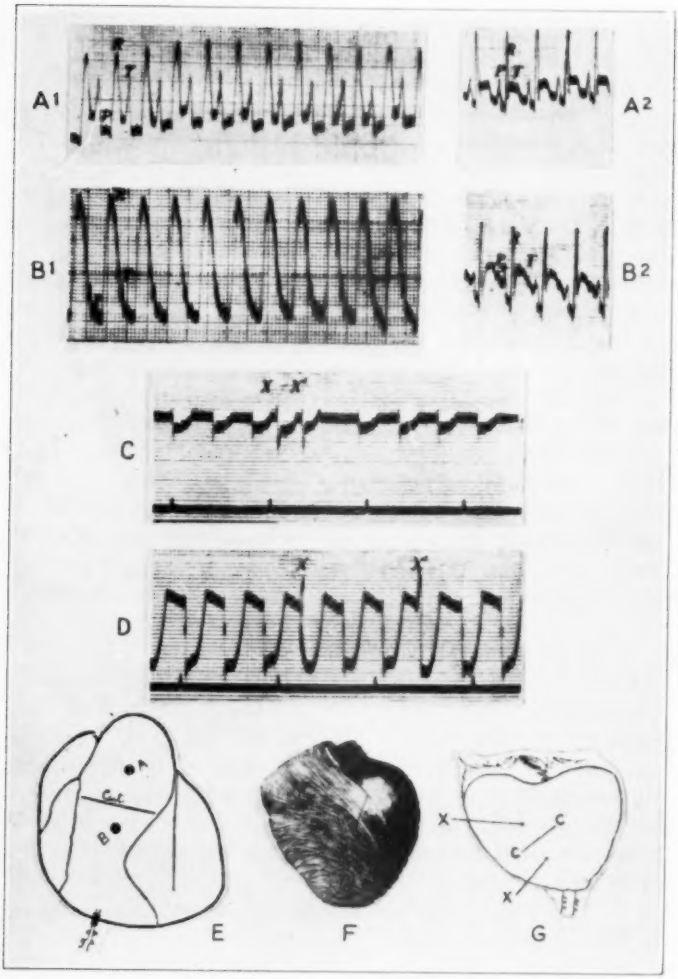

FIG. 1.—A^1, Electrocardiogram with direct contacts placed at points x—x^1 on the heart (as in insert G). Time intervals are $\frac{1}{5}$ second each. A^2, Simultaneous Lead 2, for additional "control." B^1—B^2, Records from above leads taken after cutting the muscle transversely between the take-offs (cut shown as line c—c in insert G), each differing from control above it. C, Direct leads from another muscle on the surface of the same heart, showing two excited beats. D, Same leads, after transverse section of the muscle between. Note that both normal and excited beats are altered and prolonged. E, Diagram from Lewis, showing the position of electrodes and the direction of the "cut" in his experiment. F, Drawing by Mall, showing diagonal course of surface muscles, indicating that Lewis did not have his two leads on the same bundle and that he did not completely transect any bundle. G, Location of leads at x—x^1 in our experiment.

These data indicate that in the superficial sinospiral muscle, *if an initial lesion involves the entire cross section* of the muscle at the apex, a further lesion of the uninjured portion of the muscle will not cause a further change in the electrocardiogram.

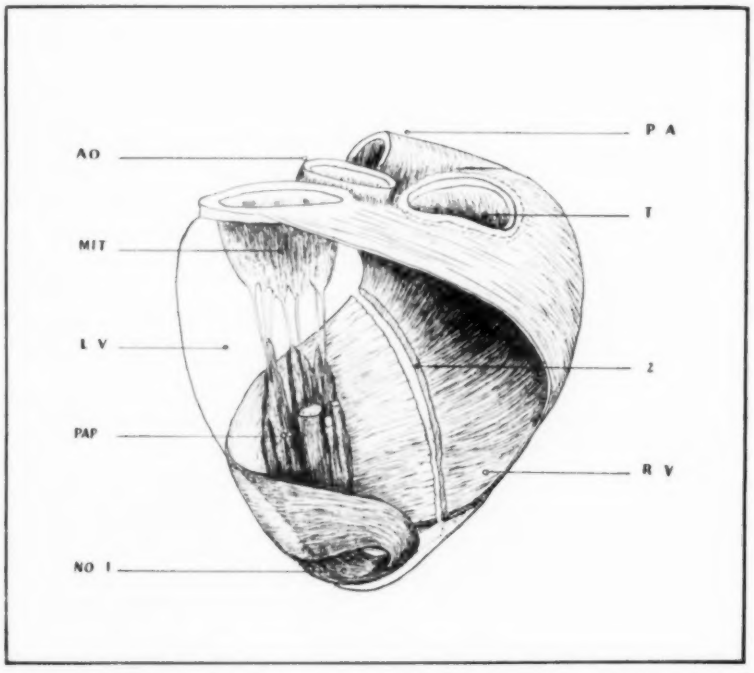

FIG. 2.—Posterior view of the superficial sinospiral muscle. *AO*, Aorta; *MIT*, mitral valve; *L V*, left ventricle; *PAP*, anterior papillary muscle; *P A*, pulmonary artery; *T*, tricuspid opening; *R V*, right ventricle. *No. 1*, Locus of apex muscle lesion, by local vessel ligation, thus rendering anemic the central portion of this muscle. *No. 2*, Locus of subsequent lesion, by transection, which initiates no further modification of the E.C.G.

Discussion.—This observation is hard to explain if one accepts the theory of radial penetration of the excitation through the thickness of the walls of the ventricles. If this radial penetration were a fact, one would expect that even though the apex of the superficial sinospiral were injured, a lesion in its course over the external surface of the ventricle would produce a further electrical change. Recently Hill[20] has suggested that the immediate effect of coronary thrombosis upon the electrocardiogram is due to an injury current. If this were the only explanation, then a second injury should cause an increased effect, which is not the case in this experiment. On the other hand, if conduction in the ventricle is not radial, but is parallel to the direction of the muscle fibers of

each muscle bundle, then one would expect that the lesion at the apex would produce the total change possible and that further lesions in portions of the muscle where the blood supply is intact would have no effect.

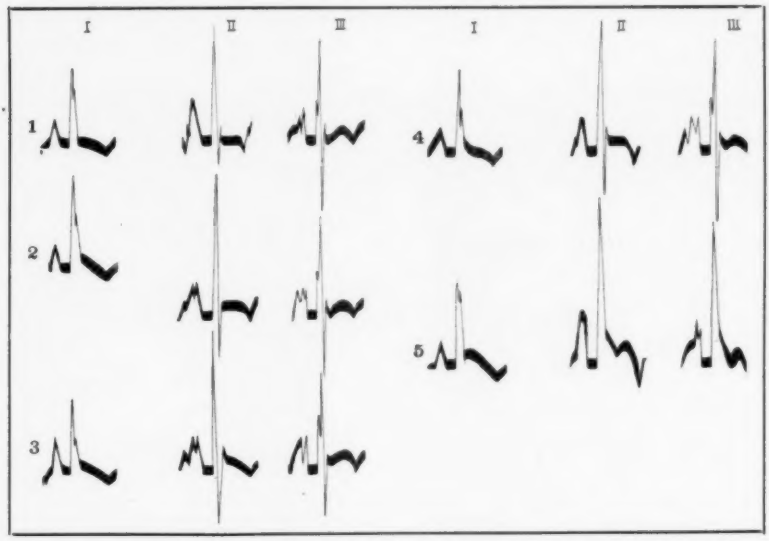

FIG. 3.—Three standard leads showing the successive effects of several procedures on the superficial sinospiral muscle in a single heart. *1*, Control with heart exposed *2*, control with compression of a few muscle fibers; *3*, apex blood supply ligated (Fig. 2); *4*, transverse cut of muscle; *5*, interruption of the main Purkinje branches to this muscle.

Lewis[4] considered the possibility of conduction by way of the muscle bands and decided against this interpretation. The estimation of conduction rates in the ventricle, upon which his theory is based, is made only from the excited beats, and some of these rates are excluded. The more rapid rates of 1200 to 1500 mm. per second were found over the right ventricle, where he believed the conduction was through the Purkinje substance. The slower rates were obtained from the left ventricle, where he assumed only muscle tissue was involved. The work of Todd[12] and Abramson[15] shows that this assumption is unwarranted, for the Purkinje fibers ramify throughout the muscle of the left ventricle as well as that of the right. Lewis[4] gives data for transmission with leads parallel to the fibers and transverse to the fibers for both natural and excited beats. The rate for transverse conduction is slower both in excited and in natural beats. These differences in conduction deserve more emphasis than was originally given them. Such data would support the opinion that conduction is along the direction of the muscle bundles.

Wiggers,[21] studying the response of the mammalian ventricle to surface stimuli, found that the "pressure maximum" of beats excited at the surface was always less than that of normal beats. In explaining the results of his study, he suggests (p. 376): "While this double contraction process also contributes to the decrease in total tension developed, evidence is cited that this is further influenced by the abnormal directional spread of impulses over the conducting system. *Such changes in distribution (Fig. 4) may alter the order in which the muscle scrolls are excited* (italics by author) and this in turn may affect the effectiveness of contraction of the entire ventricle as gauged by tension development. If there were "radial" penetration, the order of the involvement of the scrolls should be unimportant.

The consistency of results obtained in these experiments suggest that at autopsy, in order to correlate pathology with clinical evidence, lesions should be described with reference to the component muscles of the ventricle rather than located topographically.

Conclusions. 1. If the fibers of a ventricular muscle are cut transversely a characteristic change in the form and in the time relations of the electrocardiogram result.

2. Electrocardiograms of muscle lesions are of the "coronary" type.

3. Various types of injury to a given muscle, such as compression of the tissue, interruption of the blood supply, cutting the band transversely, or intraventricular interruption of the Purkinje supply to the muscle, all produce a result typical for that muscle.

4. Data accumulating suggest that impulse conduction is parallel to the direction of fibers of the ventricular muscle bands.

Acknowledgment is gratefully made to the Committee on Scientific Research of the American Medical Association, to the Hendricks Fund of Syracuse University, and to Dr. R. C. Robb who gave technical assistance in all the recent experiments and made the drawing of Figure 2.

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CLINICAL SIGNIFICANCE OF THE M OR W SHAPED Q–R–S COMPLEX IN LEAD II OF THE ELECTROCARDIOGRAM.

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A search of the literature regarding the significance of *M* and *W* shaped *Q-R-S* complexes of low amplitude in Lead II of the electrocardiogram failed to yield any information on the subject. Our attention had been directed to complexes of this type because of the presence of a *W* wave in Lead II of the electrocardiogram obtained from a patient with probable coronary occlusion. At the time, no significance could be attached to this finding although it was the only definite abnormality noted; subsequent observations, however, indicated its importance.

The present report deals with *Q-R-S* complexes in Lead II having the following characteristics:

1. The amplitude does not exceed 5 mm.
2. The complex is definitely *M* or *W* shaped throughout the tracing.
3. All the components of the complex are above the base line in the *M* shaped complexes, and below the base line in the *W* shaped complexes.
4. Occasionally there is a deflection either preceding or following the *M* or *W* shaped part of the complex, opposite in direction to its associated *M* or *W* shaped component.
5. The duration of the *M* or *W* shaped part of the complex is at least 0.08 sec. (Fig. 1, *A* and *B*).

Complexes bearing certain resemblances to the above but excluded from this group are shown in Fig. 2. Their possible relationship

to the complexes under consideration is discussed later in connection with changes in form of these complexes.

The material is, for the most part, the same as that used in the study of the significant *Q* III wave.[1] It is arbitrarily divided into six groups: I, 960 college students with presumably normal cardiovascular systems;* II, 117 college athletes;* III, 145 railroad executives; IV, 116 cases with the anginal syndrome; V, 4450 electrocardiograms taken in the years 1927 to August, 1932 inclusive; VI, 25 cases with *M* or *W* waves not included in the above groups.

There is no overlapping in Groups I, II and VI. Cases in Groups III and IV which happened to be studied within the time limit of Group V are included in that group.

Groups I, II and III. There was no instance of an *M* or *W* complex, which completely satisfied the criteria stated above.

Group IV. There were 5 records showing this complex. Two of these patients died following coronary occlusion during their stay in the hospital; 2 gave a history suggestive of a coronary occlusion; of these 1 has since died and the other is incapacitated because of pain on effort. The 5th patient died suddenly (Fig. 3).

A significant *Q* III wave was the only other electrocardiographic abnormality noted in 1 case; 1 showed a flat *T* wave in Lead II and in 1 a low *T*-2 was associated with a significant *Q* III. Two showed *T* wave inversion and slurred *Q*-*R*-*S* complexes.

Group V. In Group V there were 21 records showing this complex in Lead II, including the 5 in Group IV. The diagnoses† made in the 16 remaining cases are as follows: Cerebral thrombosis 1, myocardial disease with decompensation 4, coronary occlusion 3, rheumatic heart disease 1, syphilitic cardiovascular disease 3, hypertension and/or arteriosclerosis 3, unknown 1. The patient who had cerebral thrombosis cannot be traced. Of these 16, 10 are dead, 5 are more or less incapacitated (and from the clinical findings appear to have a poor prognosis). One patient is comparatively free of symptoms but has bundle-branch block. Only 1 of the 10 fatal cases lived more than 2 years after the taking of the electrocardiogram showing an *M* or *W* wave. This patient suffered from a coronary occlusion in 1925. At that time the electrocardiogram was abnormal but an *M* or *W* complex was not present in Lead II. In April, 1927, his electrocardiogram showed an *M* complex in Lead II; death from cardiac decompensation occurred in June, 1929. In 4 instances death took place within 6 months and 1 of these fatalities occurred on the operating table. The patient, a man aged 50, had complained of upper right abdominal pain and had symptoms suggestive of cholecystitis. At operation, however, a

* These tracings were made available through the courtesy of Dr. Francis C. Wood.

† The diagnoses given are those of the hospital records. In some, the history suggested a coronary occlusion but sufficient data were not present to warrant a definite diagnosis.

normal gall bladder was found and no abnormal condition sufficient to explain his symptoms was disclosed. While the abdomen was being closed, the patient suddenly died. Postmortem examination was not permitted. In reviewing the history and clinical and laboratory findings of this patient, the *M* wave in Lead II was the principal finding which would point to the heart as the cause of his symptoms. Although there is no proof that a cardiac accident was responsible for his death, its suddenness and the lack of any other explanation suggested this possibility.

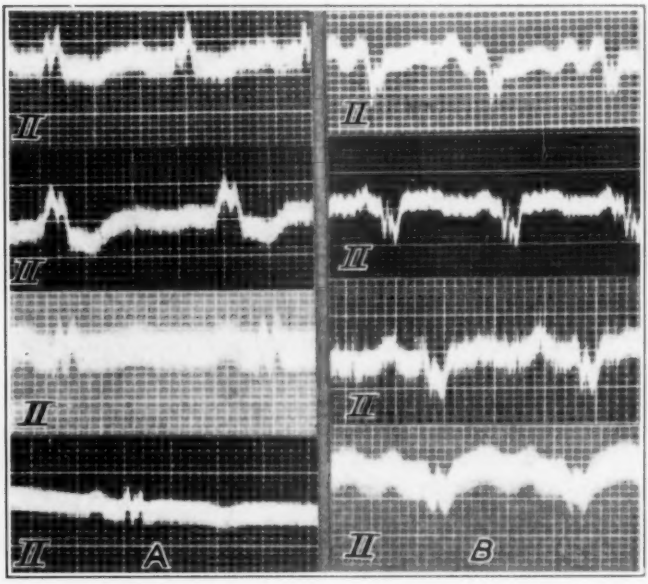

FIG. 1.—*A*, Lead II of four records, showing *M* type of *Q-R-S* complex. *B*, Lead II of four records showing *W* type of *Q-R-S* complex. Note splitting of middle limb in second tracing.

Four of the 5 patients who are known to be alive were first observed during the year preceding the study of this group. The 5th patient had coronary occlusion in 1927 from which he recovered, although he is more or less incapacitated.

Among the 16 cases, the electrocardiogram showed no definite abnormality in 1 instance, except for the *M* or *W* wave; 1 record showed a flat *T* wave in Lead I; the *T* waves were inverted in 2 leads in 5 cases; 4 showed inversion of *T* waves and slurred *Q-R-S* complexes. There were 4 records showing bundle-branch block and 1 of complete block.*

* The electrocardiograms of the 5 patients who were alive are all abnormal—2 show bundle-branch block, 1 complete *A-V* dissociation and the other 2 marked *Q-R-S* changes and *T* wave inversion following coronary occlusion.

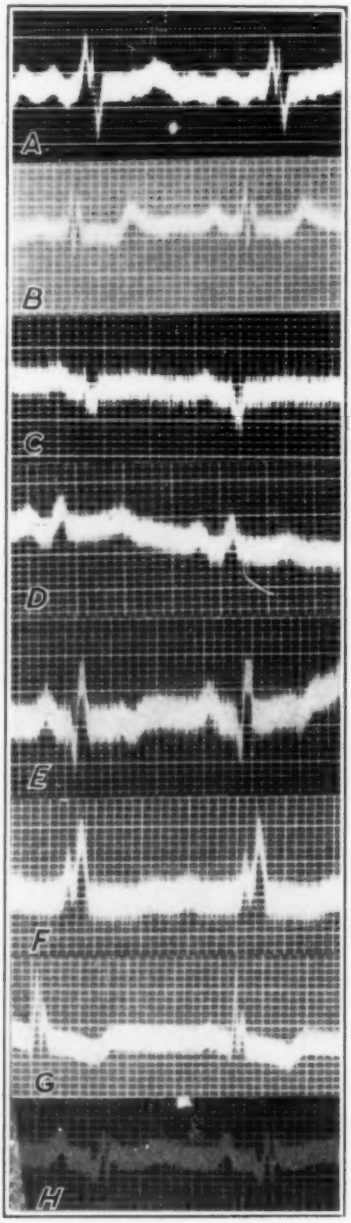

FIG. 2.—Lead II of eight records in which *Q-R-S* complex simulates *M* or *W* type of complex.

Group VI. In this group are 25 records showing an *M* or *W* wave but not included in any of the above groups. All were taken within the past 2 years. Twenty cases were diagnosed clinically as having coronary occlusion. In Figs. 4 and 5 are the electrocardiograms of 2 of these cases taken before and after the occlusion. The 21st case gave a history of attacks of substernal pain but died following an embolus which occluded the aorta at its bifurcation. At postmortem the heart muscle was found "pale, grayish, and extremely friable." No evidences of an old or recent coronary occlusion was found. Another case was that of a man aged 61,

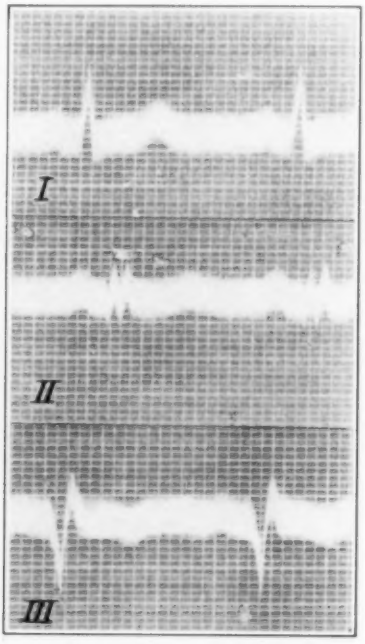

Fig. 3.—*M* shape *Q-R-S* complex in electrocardiogram of man with anginal syndrome. Death was sudden.

with syphilitic cardiovascular disease. Another patient had hypertension with blood pressure figures averaging about 230/130.

The 24th and 25th cases are obscure and have recently come to our attention. A young woman, aged 20, had vague complaints referable to the gastro-intestinal tract. An enlarged heart was discovered during routine examination. Auscultation revealed a third sound falling in early diastole over the body of the heart; the significance of which was in doubt, although the majority of observers regarded it as the opening snap of mitral stenosis. The electrocardiogram and orthodiagram are seen in Figure VI. No definite

diagnosis has been made but there can be little doubt that the heart is abnormal. The age of the patient, the lack of cardiac symptoms, the insignificant past medical history, and the large abnormally shaped heart suggest the possibility of a congenital lesion.

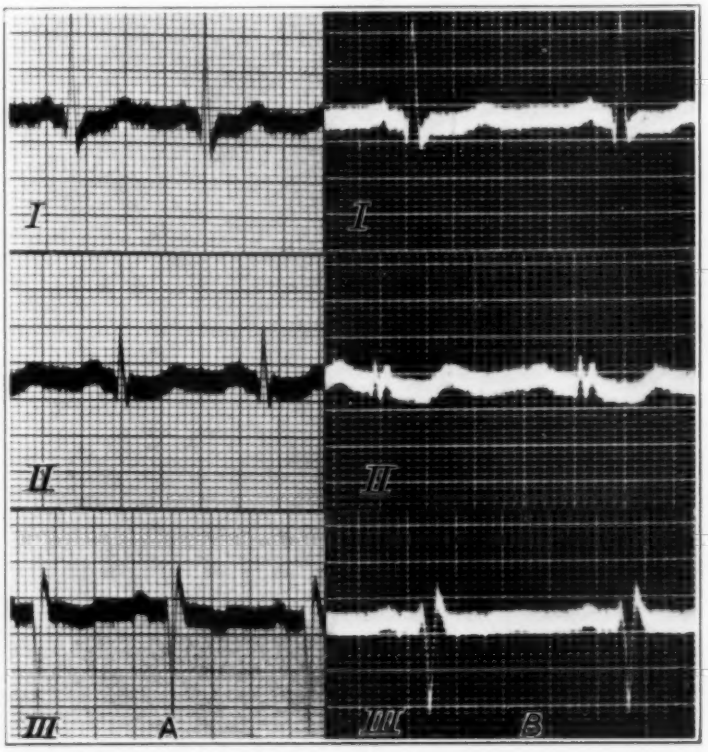

FIG. 4.—*A*, Electrocardiogram of man, aged 50. *B*, Electrocardiogram of same patient taken after possible coronary occlusion and about 2 years after *A*. Death occurred within a year after taking of *B*.

The 25th case was a man aged 35 who complained of palpitation and for no apparent reason was tired and exhausted toward evening. Examination failed to disclose any cardiovascular abnormality although the electrocardiogram showed low and slurred *Q-R-S* complexes in all leads and an *M* wave in Lead II. His symptoms improved and several months later his electrocardiogram failed to show the *M* wave.*

* In several cases of coronary occlusion the *M* and *W* wave in subsequent electrocardiograms have been replaced by complexes similar to those in Fig. 2. It is, therefore, probable that many cases showing a notched or split *Q-R-S-2* have at some time after the occlusion shown an *M* or *W* wave in Lead II.

Nine of the 25 patients in this group are dead but it is of interest that 14 of the 16 alive were first observed during the past year and 13 of these 14 have had coronary occlusion. The remaining 2 cases are the obscure cases described above. In almost all the cases with

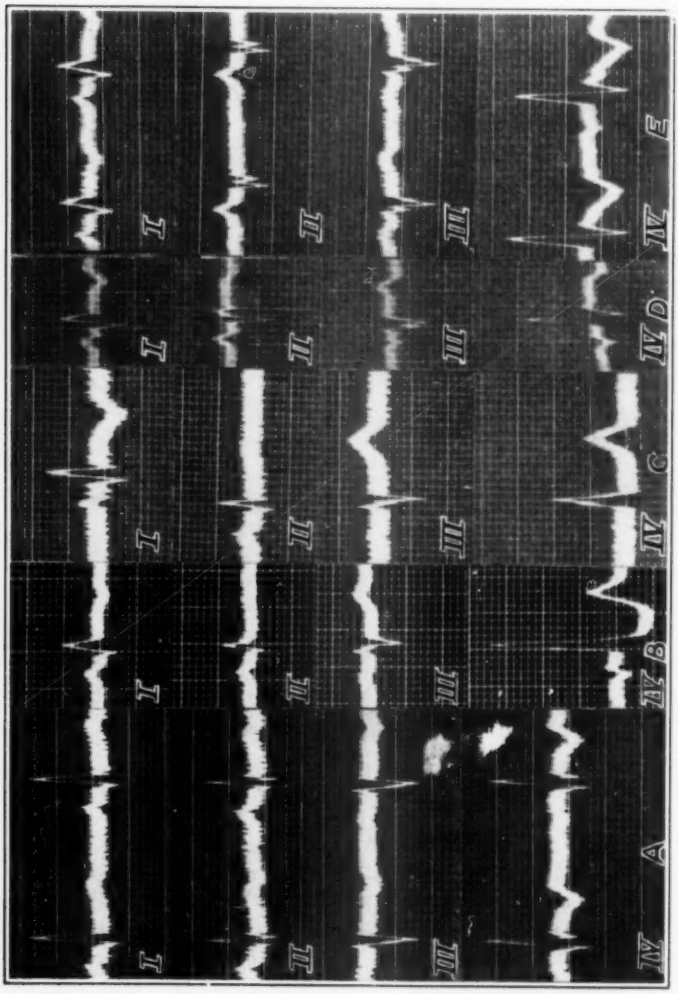

FIG. 5.—A, Electrocardiogram of man, aged 58, with anginal syndrome. *B*, 1 week after occlusion. *C*, 7 weeks later. *D*, 2 days after second occlusion and 13 months after *C*. *E*, 9 weeks later, showing formation of W wave in Lead II.

coronary occlusion, the *M* and *W* waves were observed 4 weeks or more after the occlusion. However, in several cases it has been observed immediately after.

In no case of this group showing *M* or *W* waves could the electrocardiogram be considered normal in other respects. However,

in 11, the other changes were either slight or inconclusive. In 1 case a significant *Q*-III wave was the only abnormality noted; another showed low *Q-R-S* complexes; in 2 cases the *Q-R-S* com-

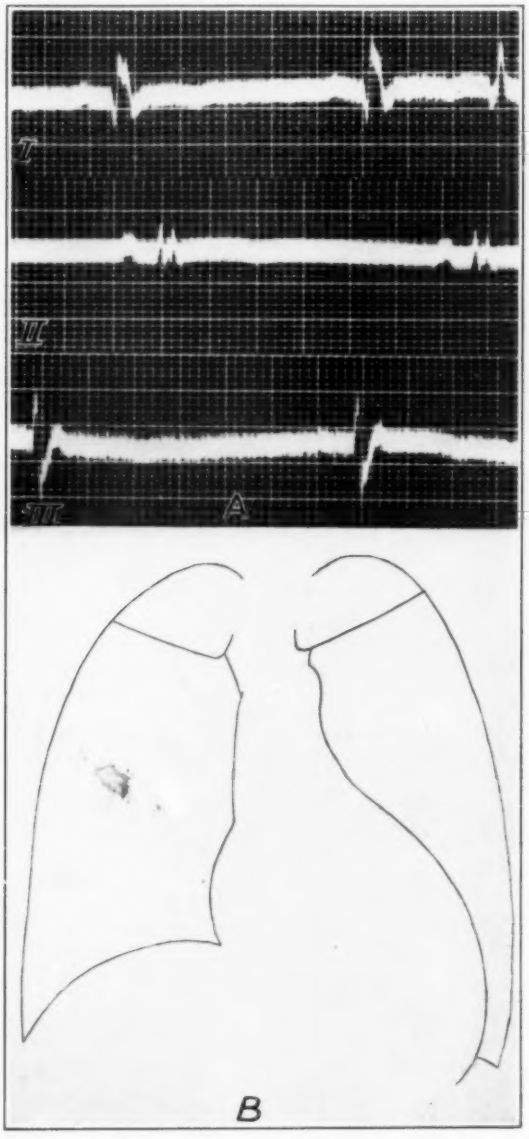

FIG. 6.—*A*, Electrocardiogram of young woman, aged 20, showing *M* wave in Lead II. There are no complaints referable to the cardiovascular system. Diagnosis obscure. *B*, Orthodiagram of same patient.

plexes were somewhat slurred; 1 case showed a *Q-R-S* complex of 0.11 second; in 3 cases *T* was upright but of low amplitude; 1 tracing showed the *S-T* interval raised (1.5 mm.) in Leads II and III; in 1 instance the record showed a flat *T*-2, an inverted *T*-3 and

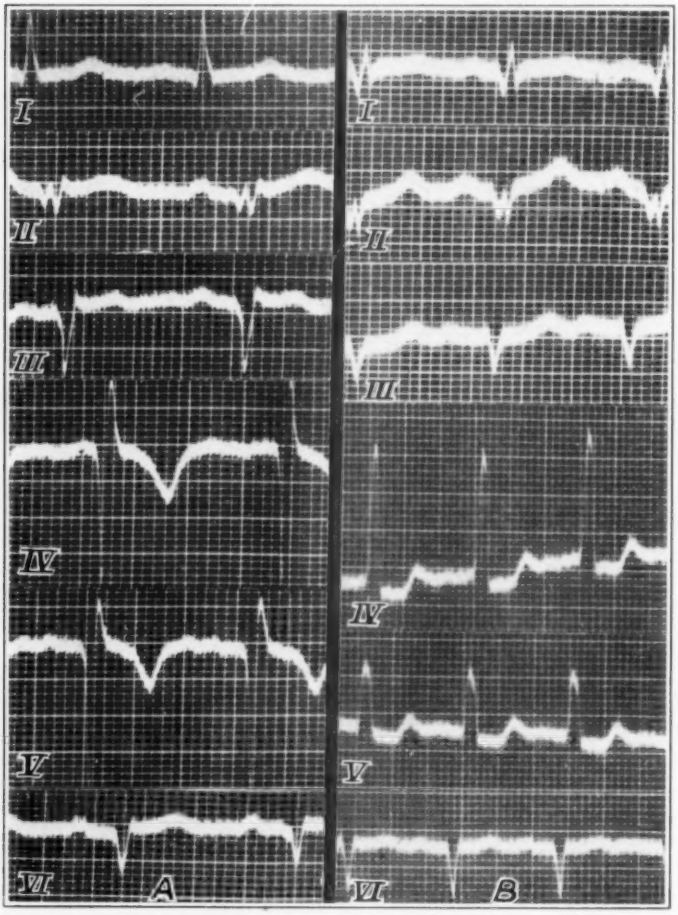

FIG. 7.—*A*, Electrocardiogram of man, aged 49, who has recovered from a suspected occlusion of the right coronary artery. Chest leads are normal. *B*, Electrocardiogram of man, aged 59, who has recovered from a suspected occlusion of the left coronary artery.

numerous ventricular extrasystoles; another case showed a *Q*-III wave and a *Q-R-S* complex of 0.11 second. The remaining 14 cases showed various *T* wave and *Q-R-S* complex changes indicative of severe myocardial disease.

Discussion. The infrequency of an *M* or *W* wave in electrocardiograms of individuals with presumably normal hearts and conversely the finding of cardiac damage in a vast majority of cases in whom the electrocardiogram shows this wave, suggests its importance.

Of the 46 records showing an *M* or *W* wave 28 were from patients suspected of coronary occlusion and the histories of some of the remainder also suggested coronary occlusion but sufficient evidence was not present to warrant a definite diagnosis. The latter were divided as follows: Cardiovascular syphilis, 4; hypertension and/or

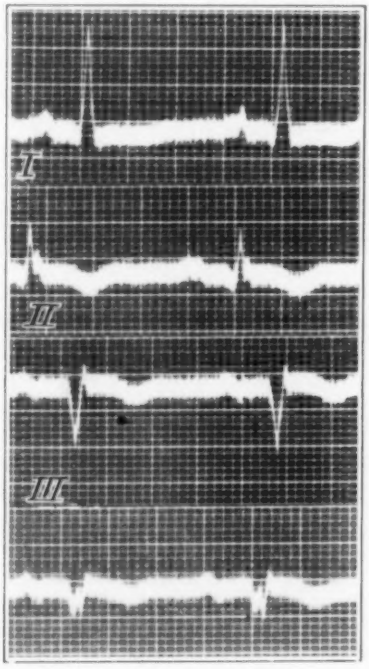

FIG. 8.—Electrocardiogram of man, aged 64, who had recovered from occlusion of right coronary artery; *W* wave in unconventional lead (right arm electrode at angle of scapula and left leg electrode in place).

arteriosclerosis, 4; myocardial disease—etiology unknown, 4; rheumatic heart disease, 1; cerebral thrombosis, 1; unknown, 4.

A study of the cases showing an *M* or *W* wave suggests that an intraventricular conduction abnormality as a result of myocardial disease is responsible for its production in most cases. Its comparative frequency in cases of coronary occlusion and in patients whose electrocardiograms show bundle-branch block supports this view. Unfortunately necropsy was performed in only 3 cases as nearly all of the patients died outside of the hospital, but in the 3 cases, myocardial damage was extensive.

From the electrocardiographic point of view, tracings showing an *M* or *W* shaped *Q-R-S* complex in Lead II can be divided into two groups: (1) those showing other abnormalities which have proven of prognostic significance, such as inverted *T* waves, bundle-branch block and complete heart block; (2) those records either not showing other definite abnormalities or in which the changes from the normal were not great.

The prognostic significance of electrocardiograms showing inverted *T* waves in the various leads, bundle-branch block and complete heart block has been established. Of the 46 tracings showing an *M* or *W* complex in Lead II, 30 belong to this group and it is doubtful whether the *M* or *W* complex adds to their prognostic significance. However, the fact that the majority of records showing an *M* or *W* wave in Lead II are from patients who have had coronary occlusion, may, in certain cases showing atypical electrocardiograms, be an aid in diagnosis. This is especially true in cases of right coronary artery occlusion in whom the chest leads are sometimes normal and also in the chronic stages of the disease during which the electrocardiographic changes may not be characteristic (Fig. 7, *A* and *B*).

However, the importance of the *M* or *W* complex must be determined by study of patients whose tracings are otherwise within normal limits or show only minor changes to which serious prognostic significance cannot properly be attributed. Of the 16 cases in this group 1 showed no definite abnormality, 5 had low (but not inverted) *T* waves in a single lead; 2, significant *Q*-III waves, and 1 showed a significant *Q*-III wave associated with a low but upright *T*-2, and 1 showed low *Q-R-S* complexes. Two cases showed slight slurring of the *Q-R-S* complexes, 1 slight elevation of the *S-T* interval, 2 showed a *Q-R-S* complex of 0.11 second, 1 of which was associated with a *Q*-III wave and 1 had a flat *T*-2, inverted *T*-3 and numerous ventricular extrasystoles. Eight of the above 16 patients died within a period of 2 years after the *M* or *W* complex was first observed; 1 patient has survived 5 years but is incapacitated because of pain on effort. The remainder, including the case with apparently no cardiovascular disease, have recently come under observation.

From the diagnostic point of view, Group VI is the most important. The patients have been more thoroughly studied and in a number, chest leads have been taken in an attempt to arrive at a more definite diagnosis. The frequency of coronary occlusion (80%) in this group is sufficiently great to suggest that these waves have some diagnostic value, their relative frequency exceeding that of the significant *Q*-III in the anginal syndrome as noted by various studies: Pardee 63%,[2] Willius[3] 38%, Zisken[4] 14%, Strauss and Feldman[5] 16%, France[6] 45%, Edeiken and Wolferth[1] 29%. When significant *Q*-III waves follow coronary occlusion they indicate infarction in

or near the posterior part of the interventricular septum. On the other hand, *M* or *W* waves may be associated with either anterior or posterior infarction.

The electrocardiograms of many of the patients with coronary occlusion were first taken after the occlusion occurred and it is therefore impossible to state whether the *M* or *W* wave preceded or was the result of the infarction.

However, in 2 cases (Figs. 4 and 5) in which the electrocardiograms were taken before and after coronary occlusion, the *M* or *W* wave followed the occlusion and in 1 of these cases it appeared only after the second occlusion. In 2 other cases in which electrocardiograms were taken at intervals after the occlusion, a *W* wave appeared after 6 weeks in 1, and 3 months in the other. In both cases it was not present in earlier or later electrocardiograms.

The *M* and *W* waves are not, therefore, in all cases permanent changes and it is possible that some of the tracings in which *Q-R-S* complexes in Lead II resemble the *M* or *W*, but are not included because they do not conform to the criteria stated (Fig. 2), may also be of equal significance, since one electrocardiogram may show one of these types of *Q-R-S* complexes whereas another taken at a later date may show the other type of coronary occlusion.

It is also probable that a change in electrical axis may cause some complexes of the type shown in Fig. 2 to assume an *M* or *W* form. Two cases, not included in this study, showed a slurred *Q-R-S* complex in Lead II which was very suggestive of an *M* wave in several complexes. In an unconventional lead, however, (right arm electrode at angle of left scapula and left leg electrode in place) an *M* or *W* wave was present throughout the tracing (Fig. 8). Both cases had a history of coronary occlusion; 1 patient is alive, the other died of pneumonia. However, the unconventional lead employed in these 2 cases has an axis about midway between Lead II and III and, although the *M* or *W* wave in these two instances appears significant, it is obvious that conclusions cannot be drawn from the findings in 2 isolated cases.

Complexes of the *M* or *W* type occur frequently in Lead III and occasionally in Lead I. Although certain cases with undoubted coronary occlusion have shown an *M* or *W* wave in Lead III, complexes of this description are seen in tracings from presumably normal individuals.

Three instances of the *M* or *W* complex occurring in Lead I have been observed in this study. Two of these patients had suffered from a coronary occlusion; 1 died 6 weeks after the tracing was taken, the second is incapacitated because of pain on effort and the third suffered from rheumatic heart disease with mitral stenosis and regurgitation. Death occurred as the result of a pulmonary embolism 11 days after the taking of the tracing.

Summary and Conclusions. 1. An *M* or *W* wave in Lead II of the electrocardiogram having the characteristics defined in this paper has *not* been observed in tracings of 1077 presumably normal adults.

2. It was seen 5 times (4.3%) in 116 patients with the anginal syndrome. After a period of 3 years, 4 of the 5 are dead, the other incapacitated.

3. In 4450 unselected electrocardiograms of hospital and clinic patients, the *M* or *W* wave was seen in 21 tracings (0.47%). Of these patients 14 are dead, and 6 show clinical evidence of severe myocardial disease; 1 cannot be traced. The electrocardiograms of 2 of the 6 patients who are alive show bundle-branch block, 1 complete A-V dissociation and the other 3 have had a coronary occlusion and are more or less incapacitated. Only 2 of this group have lived more than 3 years after the *M* or *W* wave was first observed and both of these are incapacitated because of pain on effort.

4. Of 25 isolated cases observed during the past 2 years, 20 (80%) were from patients with coronary occlusion. Nine of the patients are dead; 13 of the remainder are from the groups suspected of having had a coronary occlusion, 1 suffered from hypertension and the 2 remaining cases are obscure and in 1 of these no other evidence of cardiovascular disease was found.

5. In most cases the *M* or *W* wave is probably due to an intraventricular conduction abnormality as a result of myocardial disease. Pathologic changes were widespread in the 3 cases in which necropsy was obtained. It is possible, however, that a congenital anomaly of conduction may occasionally produce complexes of this type.

6. In some cases the *M* or *W* complex has been present throughout the entire period of observation. In others, it has been relatively transient. Its appearance time following coronary occlusion is variable, the range observed in serial electrocardiograms being 1 day to 3 months.

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BOOK REVIEWS AND NOTICES.

1. A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. Cowdry, Professor of Cytology in the School of Medicine, Washington University, St. Louis. Pp. 503; 242 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $5.50.
2. Essentials of Histology. By Sir E. Sharpey-Schäfer, F.R.S., Formerly Professor of Physiology in the University of Edinburgh. Thirteenth edition edited by H. M. Carleton, M.A., B.Sc., D. Phil., Lecturer on Histology in the University of Oxford, Research Fellow of New College, Oxford. Pp. 618; 721 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $5.00.
3. A Textbook of Histology. By Alexander A. Maximow, Late Professor of Anatomy, University of Chicago, and William Bloom, Associate Professor of Anatomy, University of Chicago. Pp. 662; 530 illustrations, some in colors. Second edition, completely revised. Philadelphia: W. B. Saunders Company, 1934. Price, $7.00.

Among the new textbooks and new editions that annually herald the advent of the medical school year, those on histology are especially prominent this year. Sharpey-Schäfer's "Essentials," which in a half century has reached the enviable distinction of 13 editions and Maximow's fine volume, reflecting ably the brilliant studies of that lamented investigator, are now joined by Cowdry's text, written with all the charm and freshness of viewpoint of that well known prolific pen.

It would seem profitable to consider the 3 volumes together. Immediately one notices the effect of the world's economic situation. The Maximow has been reduced by 170 pages at a saving to the buyer of $2.00. The English book (though costlier and larger than earlier editions) sells for less than the others, at a very modest price as medical textbooks go; while Dr. Cowdry's recognition of the pedagogic need for rigid selection has also permitted the attainment of a low price. This gives a cost for the 3 books of, 1.06, 0.81 and 1.10 cents per page respectively; and, while the Essentials' page is smaller in size, this is balanced by the use of smaller, though legible, type. One would indeed be embarrassed as to which to select for the average student. All are excellent books, clearly written, by masters in their own particular field, all are well illustrated and printed and all have recognized the need for stressing the relation of form to function. Each—as is inevitable, nay, even desirable—is especially strong in fields in which the author has chiefly labored. Thus Maximow's sections on the blood forming and destroying tissues are noteworthy, whether or not one agrees with his decided and rather extreme views on the subject. The Cowdry volume is especially strong on "The Blood, the Principal Integrator" and on the endocrine organs—these two sections together comprising a full quarter of the text. A surprising exception, is the relatively short space devoted in the Essentials to the endocrine organs; here, however, the lessons on nervous tissues and the central nervous system are unusually detailed, comprising more than one-fifth of the total space. It would seem, then, that the deciding factor for a prospective purchaser might well depend on the field in which his own chief interest lay. The illustrations are most numerous in the Essentials—least so in "Cowdry;" the former, however, are in the more diagrammatic style in vogue in English textbooks, while the quality of the latter is unusually high, both in subject and in execution. Cowdry has

sensibly omitted the simpler, hackneyed pictures that the student can easily comprehend from his own slides. The Maximow illustrations, less reduced in number from the first edition than the text, are good and more than twice as numerous as the Cowdry. Too many, however, especially in the Special Sense sections, are "redrawn from" or "after" other writers. "Cowdry" has a useful 21-page combined bibliography and author index; "Maximow" has wisely included appropriate references at the end of each chapter. None of these books meets the need for a reasonably complete presentation of human histology—and none of them is intended to do so. All 3 accomplish ably the purpose for which they were written.

E. K.

A Textbook of Pathology. By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), Dipl. Psych., F.R.S.C., Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg. Pp. 1047; 416 illustrations and 8 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $10.00.

When many medical publications are keeping in step with the times by retrenchments in size, it is a pleasure to find a new edition required in the short space of 2 years, and to see it augmented by 100 pages and more than 100 engravings. It is also a pleasure to see that morbid anatomy, a subject dead only "in the hands of those whose dull minds would take the breath of life from the most vital subject," requires expanded treatment after such a short period. In addition to really extensive revision, the following topics have been added: bacterial infections, immunity and allergy, trauma, von Gierke's glycogen storage disease, lead poisoning, localization of infection, rhinosporidiosis, Oroya fever, causation of anginal pain, tobacco hypersensitiveness, medionecrosis of the aorta, pneumonia in the newborn, duodenitis, stasis gall-bladder, chronic Bright's disease, renal infantilism, arrhenoblastoma, sweat gland carcinoma of the breast, lateral aberrant thyroid tumors, pituitary basophilic invasion, monocytic leukemia, the St. Louis type of encephalitis, bone tumors, together with new chapters on heredity and constitution and on diseases of the teeth. In a field already fortunate in its textbooks for students, this book has now firmly established itself as a leader.

E. K.

Elektrokinetic Phenomena and Their Application to Biology and Medicine. By Harold A. Abramson, M.D. Pp. 331; 106 illustrations. New York: The Chemical Catalog Company, Inc., 1934. Price, $7.50.

Thoroughly qualified both as experimenter and student of the literature, the author has presented the subject of electrokinetic phenomena in concise and readable form. It was observed by Reuss, in 1808, "that a direct electric current could forcibly transport the charged water molecules through a porous quartz or clay diaphragm." This phenomenon is known as electro-osmosis. The converse phenomenon, electrophoresis or cataphoresis, the electric transport of particles suspended in liquid, was observed but not understood by Reuss. From this beginning the author traces the development of the subject up to the present day. Of particular interest are the applications of electrophoresis to modern immunology. Measurement of the change in velocity in an electric field, of bacteria and other cells, brought about by antibodies, has thrown much light on the nature of these substances. To what extent electric charge of bacteria varies with virulence appears a promising field for further investigation. The reader is aided by an appendix in which the mathematical symbols are collected and defined.

M. McM.

LEHRBUCH DER INNEREN MEDIZIN, VOLUMES 1 AND 2. By DR. G. VON BERGMANN, with DRS. F. STROEBE (BERLIN), A. DOERR (BASEL), H. EPPINGER (VIENNA), FR. HILLER (MÜNCHEN), G. KATSCH (GREIFSWALD), L. LICHTWITZ (with A. RENNER) (NEW YORK), P. MORAWITZ (LEIPZIG), A. SCHITTENHELM (with E. HAYER) (KIEL), R. SIEBECK (HEIDELBERG), R. STAEHELIN (BASEL), W. STEPP (BRESLAU), H. STRAUB (GOETTINGEN), S. J. THANNHAUSER (FREIBURG I. BR.). Pp. 1708; 290 illustrations. Berlin: Julius Springer, 1934. Price, Rm. 45.

SIXTEEN authors under the capable leadership of Professor von Bergmann have produced what is probably the best German textbook on medicine. A two-volume work makes possible a more satisfactory presentation of the subject matter usually covered in the one volume to which all recent American texts on medicine are restricted. It permits, too, the inclusion of material not generally found in our textbooks. Worthy of mention in this regard is the introductory chapter (50 pages) dealing with such topics as the scope of internal medicine; the patient and his environment; the concept of constitution; the principles of heredity; also the chapters on the general principles of infection and immunity and of the treatment of infections (112 pages). Emphasis and clarity are enhanced by the judicious use of several kinds of type: bold face, capitals, italics, with small type in addition effecting the saving of valuable space. The illustrations, notably the many roentgenograms, are well done. The net result is a work that gives the student a broader, more philosophic viewpoint than a one-volume text can do, and at the same time does not swamp him in the mass of detail of a larger "system" of medicine. R. K.

BRIGHT'S DISEASE. A Clinical Handbook for Practitioners and Senior Students. By J. NORMAN CRUICKSHANK, M.C., M.D., D.Sc., F.R.F.P.S. (GLAS.), M.R.C.P. (LOND.), Senior Assistant to the Muirhead Professor of Medicine, University of Glasgow; Assistant Physician, Glasgow Royal Infirmary; Visiting Physician, Southern General Hospital, Glasgow. Pp. 208. Baltimore: William Wood & Co., 1933. Price, $3.75.

"THIS book has been written with the object of providing the practitioner and the senior student with a short account of the clinical application of modern views of the nature of Bright's disease." The bewildering mass of literature that has accumulated in recent years with their advances in knowledge of renal function and disease has created a real need for a digest of this material for the practitioner and student, a need which this excellent little volume is eminently qualified to fill. Chapters on the functions on the kidney, types of Bright's disease, etiology, treatment, tests of renal function, edema in Bright's disease, uremia, kidney structure, and technical details of some methods employed in estimating renal functional efficiency present these topics in a concise, adequate and lucid manner. The book is warmly recommended. R. K.

DIE OPHTHALMOLOGIE DES SUSRUTA, ETC. Heft 22 of Studien zur Geschichte der Medizin. By DR. MED. ET PHIL. A. ALBERT M. ESSER, Augenarzt in Düsseldorf. Pp. 83. Leipzig: Johann Ambrosius Barth, 1934. Price, Rm. 7.50.

IT is rather widely recognized that the history of ancient Hindu medicine is at the moment in a far from satisfactory condition. The labors of such philological historians as Reinhold Müller and the author, each working, to be sure, from different points of view, will doubtless clarify the situation ere long. On account of the long and devious course of Indian medicine,

Esser has chosen to study through various periods a cross section of the subject as treated by various writers—such as ophthalmology in this case—rather than treat of the individual or his period as a whole. This work on Susruta's Uttaratantra follows similar studies by the author on the Bhavaprakasa of Bhavamisra. The translation occupies the bulk of the monograph. E. K.

Die diätetische Behandlung der Allergie bei inneren Erkrankungen. By Carl Funck, M.D., Chief of the Section for Allergy and Disorders of Nutrition, Elizabeth Krankenhaus, Köln-Hohenlind. Pp. 92. Leipzig: Johann Ambrosius Barth, 1934. Price, Rm. 2.40.

Based on the theory (unproved) that food allergy is based on an abnormal permeability of the gastro-intestinal mucosa for unsplit protein and the subsequent failure of the hepatic barrier, with the further etiologic factor of a "can-opener, cork-screw" diet, the author propounds his therapeutic doctrine. While the book contains many things of practical value and interest, there is unfortunately much that is open to question, and vehemence of statement often takes the place of logic. The differences of German diet from ours (magnified by a "Buy-German" propaganda) greatly lessen the value of the book for American readers. R. K.

Bone Growth in Health and Disease. By H. A. Harris, D.Sc. (Lond.), M.B., B.S. (Lond.), B.Sc. (Wales), M.R.C.S., M.R.C.P., Professor of Clinical Anatomy, University College and University College Hospital, London; Hunterian Professor and Arris and Gale Lecturer of the Royal College of Surgeons, etc. Pp. 248; 201 illustrations. New York: Oxford University Press, 1933. Price, $10.50.

Divided into three parts this monograph covers: I. Arrest of bone growth in systemic disease; II. Correlation of radiological appearance and histological structure of bone; III. Recent investigations in bone growth.

The treatise is interestingly written and well illustrated. The investigative data are not always convincing nor are the conclusions at all times well founded. G. W.

The Chemistry of the Hormones. By Benjamin Harrow, Ph.D., Associate Professor of Chemistry, College of the City of New York, and Carl P. Sherwin, D.Sc., M.D., Dr.P.H., on the Staff of St. Vincent's Hospital and French Hospital, New York City. Pp. 227. Baltimore: The Williams & Wilkins Company, 1934. Price, $2.50.

So much work has been done recently upon various hormones that even research workers in this field find it difficult to keep up with more than their own specialized interests. One need only mention the constantly growing list of pituitary hormones and their relationship to the gonads, thyroid and adrenals to realize that new information has been gathered so fast that confusion was unavoidable. A short monograph which sums up the isolation, chemistry and assay of the recognized hormones is, therefore, both timely and valuable.

The work is divided into nine chapters which cover the hormones of the thyroid, parathyroid, pancreas, pituitary, adrenal, testis, ovary, duodenal mucosa and plant tissues. The authors are to be congratulated upon a judicious choice of material, resulting in lucidity which would otherwise be impossible to attain. The bibliographies at the end of each chapter are more than adequate.

Although no more is claimed for the monograph than "a *practical* book—a book of use to the laboratory worker who wishes to prepare active hormone fractions, or to isolate a chemically pure hormone," the Reviewer feels that also the clinician, mainly interested in hormones from the standpoint of therapy or diagnosis, may derive a clearer view of these substances from a knowledge of their preparation and chemistry. D. D.

BRUCELLA INFECTIONS IN ANIMALS AND MAN. By I. FOREST HUDDLESON, Department of Bacteriology and Hygiene, Michigan State College. Introduction by WARD GILTNER, Dean, Division of Veterinary Medicine, Michigan State College. Pp. 108; 24 illustrations, 2 in colors. New York: The Commonwealth Fund, 1934. (No price given.)

THE growing recognition of the importance of Brucellosis (infectious abortion, undulant fever) in human and veterinary medicine makes this monograph especially timely. The topics covered are: a brief history of the three species of Brucella; descriptions of morphology, staining and cultural characteristics; methods of isolating the organisms; the pathology of Brucella infections; diagnostic methods (agglutination, skin tests and opsonic activity); and methods of differentiating the species of Brucella. There is a bibliography of 188 titles and an index. The book is well written, statements are brief, directions clear and illustrations well chosen.

H. R.

SÉCRÉTION INTERNE ET RÉGÉNÉRESCENCE. By N. E. ISCHLONDSKY, M.D. Pp. 336; 72 illustrations. Paris: G. Doin et Cie, 1933. Price, 90 fr.

INSERTED just before the preface are over three pages of corrections of typographic errors. Thirty pages would not suffice to list the multitude of fallacies and absurdities of the text. R. K.

THE MANAGEMENT OF FRACTURES, DISLOCATIONS AND SPRAINS. By JOHN ALBERT KEY, B.S., M.D., Clinical Professor of Orthopedic Surgery, Washington University School of Medicine; Associate Surgeon, Barnes, Children's, and Jewish Hospitals, St. Louis, and H. EARLE CONWELL, M.D., F.A.C.S., Orthopedic Surgeon for the Tennessee Coal, Iron and Railroad Company, Birmingham, Alabama, etc. Pp. 1164; 1165 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $15.00.

PROBABLY no recent book covers the field of fractures and joint traumata so thoroughly. The book is of particular value in that it is composed entirely of the personal experience of two surgeons who have had the opportunity to handle an enormous number of cases. The details of treatment are personal and not encyclopedic; the illustrations are good and the general composition of the book satisfactory. G. W.

PATHOLOGIE DER MITOSE. By GEORG POLITZER, Privatdozent der Embryologie an der Wiener Universität. Band 7 of Protoplasma-Monographien. Pp. 238; 113 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 16.20.

THIS useful booklet adequately brings together in a small but important field information not otherwise readily available. Under the headings: Morphology (pyknosis, rhexis, polarization and cytoplasmic changes), Changes

in Rhythm of Division, Cell Division in Carcinoma and in Hybrids, Actinic and Chemical Effects, The Problem of Specificity, the various abnormalities of cell division are systematically presented by one whose individual contributions to the subject has been not inconsiderable. A fifteen-page reference list facilitates more extensive study. The sections must be read in detail to be comprehended, both on account of the nature of their contents and as no summary is presented of the many observations or the conclusions to be drawn from them. E. K.

THE TEACHING OF PREVENTIVE MEDICINE IN EUROPE. (University of London Heath Clark Lectures, 1932, delivered at The London School of Hygiene and Tropical Medicine.) By CARL PRAUSNITZ, M.D. (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Hygiene in the University of Breslau. Pp. 180; 37 illustrations. New York: Oxford University Press, 1933. (Price not given.)

THIS little volume contains the Heath Clark Lectures delivered at The London School of Hygiene and Tropical Medicine by one of the foremost authorities on Preventive Medicine. The contents divide themselves into two parts: the history, philosophy and outlook of the whole preventive medicine movement, and a well chosen summary of the activities in the fields of practical hygiene and preventive medicine teaching in the several European countries.

Although the introduction mainly concerns itself with the first of these objectives, the other chapters setting forth the detailed program in each country are also flavored with the mature philosophy and conservative criticism of this distinguished author.

Professor Prausnitz rightly points out that there should be two types of training available for the future of Preventive Medicine: the training of the specialist who would pursue a career concerned with the practical applications of the State's share in the hygiene program, but even more important the imbuing of every prospective physician with the broad principles of modern Preventive Medicine so that he may apply these principles to every case in his future practice. The volume is recommended for those who desire another authoritative discussion of the methods used in European countries to insure health and sanitation and to teach the newer philosophy of Preventive Medicine. E. T., JR.

CRANIOCEREBRALE SCHEMATA FÜR DIE RÖNTGENOGRAPHISCHE LOKALISATION. By PROF. DR. A. SCHÜLLER, Consiliarius am Zentral-Röntgen-Institut des allg. Krankenhauses in Wien, und DR. H. URBAN, Assistent der Psychiatrisch-neurologischen Universitäts-Klinik in Wien. Pp. 8; 17 figures and 1 celluloid stencil. Leipzig: Franz Deuticke, 1934. Price, M. 4.

IN this pamphlet the authors describe a method for the roentgenographic localization of intracranial lesions and the determination of the relationship of pathologic processes of the calvarium to the surface of the underlying brain. The method is briefly and clearly described. The necessary cross-section and surface drawings of the brain and skull and a celluloid stencil required to employ this method of localization are supplied with the description. The method is exceedingly simple and would appear to be, as stated by the authors, sufficiently accurate for all practical purposes. The procedure is one that can be readily employed in any Roentgen laboratory, as the technique, with slight modifications, utilizes the usual views employed in head radiography. The method is recommended to those interested in the localization of lesions capable of demonstration by the Roentgen ray. K. K.

EPIDEMIC MYALGIA. BORNHOLM DISEASE. By EJNAR SYLVEST, M.D. With a Foreword by DR. TH. MADSEN, Director of the Danish State Serum Institut, Copenhagen. Translated from the Danish by HANS ANDERSON, M.D. Pp. 155. Copenhagen: Levin & Munksgaard, 1934. Price, D. Cr. 8.

ABOUT 10 years ago our Atlantic Seaboard was visited by what appeared to be a new disease with such strikingly painful symptoms that it attained prominence in the newspapers as "devil's grip;" in medical journals as epidemic pleurodynia. This monograph treats of the same disease under the name of epidemic myalgia, and traces its course through Scandinavia, England, Germany and North America, since its first recognized appearance in Iceland in 1856. A disease that has numbered over 10,000 victims in Denmark alone in recent times, even though not threatening to life, is well worth the attention here given to it. E. K.

THE LIFE OF SIR ROBERT JONES. A Biography of the World's Greatest Orthopedic Surgeon, the Friend of Crippled Soldiers and Children. By FREDERICK WATSON. Pp. 327; illustrated. Baltimore: William Wood & Co., 1934. Price, $3.75.

AFTER reading this glowing biography, it is hard to decide whether Robert Jones was greater as a scientist or as a man. Richly endowed intellectually and with the good fortune to come early under the influence of the great H. O. Thomas, Jones' genius was well prepared to utilize the unequalled opportunities of the war to advance knowledge of orthopedics to a position far beyond its previous status. Americans have good reason to be grateful for the invaluable training that he gave their orthopedists at this critical time. A highminded, optimistic humanitarian, "only easy-going so long as his principles were unchallenged," righteously indignant on occasion, but by nature patient and humorous, these are the qualities that will be recalled by his friends and patients. The story of this great life is divided into a Prelude (1857–1891); Consolidation (1891-1914); the Disabled Soldier (1914–1920); Harvest (1920–1933). The inspiration that it carries for the young medical man is hard to overestimate. E. K.

APPLIED PHYSIOLOGY. By SAMSON WRIGHT, M.D., F.R.C.P., John Astor Professor of Physiology, University of London. Pp. 604; 195 illustrations, 1 colored plate. Fifth edition. New York: Oxford University Press, 1934. Price not given.

THIS edition maintains the former purposes of this book of describing physiology from the laboratory and scientific standpoint and of adding to each subject the applications of the facts and principles to clinical medicine, explaining the signs and symptoms as far as possible. The author has made material changes to no less than forty subjects and has added a great many illustrations. The book is to be recommended for students but will be perhaps most helpful to the clinician to explain the physiologic reasons for the symptoms and signs of a particular case. The teacher of clinical medicine might well peruse the appropriate pages before giving his lecture. No subject that is truly important in human medicine has been overlooked. The physiology of the nervous system is perhaps treated with unnecessary length but, at all events, the author shows the relationship between the functions and anatomy of different parts as correlated and harmonized through the nervous connections. The author continues to use the glossary of international anatomic nomenclature, the so-called B.N.A., so that terms unusual to the readers in the United States may be easily found. Indeed, some places in the text he uses both terminologies. This new edition is a welcome one on the shelf of the practical and laboratory medical man. H. F.

THE CYCLOPEDIA OF MEDICINE. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., and A. GRAEME MITCHELL, M.D. (CHARLES E. DEM. SAJOUS, M.D., LL.D., Sc.D., Founder and First Editor). Twelve Volumes and Desk Index Volume; each illustrated with half-tone and line engravings, also full page color plates. Philadelphia: F. A. Davis Company, 1931–1934. Price, $120.00.

To review a medical book is ordinarily not so difficult a task: a careful reading and then the expression of an opinion by one qualified to do so in that field. To review a cyclopedia, however, is quite a different matter. To read word for word the twelve volumes is out of the question, let alone to presume to pass judgment on all the contents. The Reviewer therefore did two things: leaf through the volumes, page for page, reading such articles as caught his fancy; and, what is more to the point, use the books for some months as a reference work, which after all is their purpose. He was pleased with what he found: most topics were covered adequately, some exceedingly well, and only very few were disappointing. Perhaps he would have been even more pleased had he had the index volume to guide him: this has not yet appeared. Upon it will depend in no small measure the usefulness of the work, for while there is an alphabetic arrangement of the subject matter, there has not always been followed a set scheme of indexing (so one finds, *Caffeine:* see *Coffee; Calabar Bean:* see *Physostigma; Nephritis:* see *Kidneys; Blood:* see *Hematology*). The Editor has succeeded remarkably well in the difficult task of avoiding duplication and of preserving proper balance in space used by the 700 contributors. One might object, however, to the allottment of 80 pages to vascular tumors and only 23 to typhoid fever; or of 5 colums to apocynum, only 1 to allonal, and why any space at all to Adonis vernalis, or 3 columns to scoparius of which "there is now no official preparation." Hay fever has been covered twice, and physical allergy by the same author, but food allergy as a factor in headache or gastro-intestinal disorders is not mentioned. Of particular excellence are the sections on the cardiovascular system, and the gastro-intestinal tract. Weakest are pharmacology and endocrinology. The illustrations are numerous and well done. R. K.

THE PHYSIOLOGICAL EFFECTS OF RADIANT ENERGY. American Chemical Society Monograph No. 62. By HENRY LAURENS, PH.D., Professor of Physiology, Tulane University School of Medicine. Pp. 610; 104 illustrations. New York: The Chemical Catalog Company, Inc., 1933. Price, $6.00.

EXHAUSTIVE as is this substantial volume, it fails to live up to its still more exhaustive title. The discussion is limited to certain physiological effects of the wavelengths present in the solar spectrum. The effects of other radiant energy—for example, of Roentgen rays and rays from radioactive substances—are not described. Moreover, certain physiological effects of the solar spectrum, such as vision and plant photosynthesis, are scarcely mentioned. These omissions are of course quite proper, since the topics mentioned have been exhaustively dealt with in other books; but the title might have been more indicative of the content. The author has dealt in an adequate and scholarly fashion with the components of the solar spectrum chiefly in their relations to mammalian metabolism, to phototherapy, and to the production of pathological effects. Five chapters (224 pages) are devoted to effects upon metabolism, including the relationships between radiation and vitamins. Two chapters (39 pages) summarize the effects upon wounds and certain diseases, while five others deal respec-

tively with effects on the skin, the eye, the circulatory system, the blood, and body temperature, respiration and blood reaction. Photodynamic sensitization is discussed at some length and the effects upon microörganisms, toxins, proteins, enzymes, etc., are dealt with in an adequate fashion. The chapter on the physics of radiant energy includes brief descriptions of methods of measurement and an extended account of the spectral distribution of the energy from various artificial sources and of the solar radiation incident at various places and under various conditions. The mechanism of physiological action of the radiant energy is covered in nine pages, which fact strikingly emphasizes the present paucity of our knowledge of this essential subject. The primary aim of the author has been, not to write a critical review, but to compile a source book. In this rôle his volume should prove very useful. R. Z.

NEW BOOKS.

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1156; 182 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $9.00.

Benjamin Rush. Physician and Citizen (1746–1813). By NATHAN G. GOODMAN. Pp. 421; illustrated. Philadelphia: University of Pennsylvania Press, 1934. Price, $4.00.

The Radiology of Bones and Joints. By JAMES F. BRAILSFORD, M.D. (B'HAM.), M.R.C.S. (ENG.), Radiological Demonstrator in Living Anatomy, the University of Birmingham, etc. Pp. 500; 310 illustrations. Baltimore: William Wood & Co., 1934. Price, $9.00.

Franklin Paine Mall. Anatomist. By FLORENCE RENA SABIN. Pp. 342; 6 illustrations. Baltimore: The Johns Hopkins Press, 1934. Price, $2.75.

Lincoln's New Salem. By BENJAMIN P. THOMAS. Pp. 128, illustrated. Springfield, Ill.: The Abraham Lincoln Association, 1934. Price, $1.00.

Sex-Hygiene. What to Teach and How to Teach it. By ALFRED WORCESTER, A.M., M.D., Sc.D., HENRY K. OLIVER, Professor of Hygiene, Harvard University. Pp. 134. Springfield, Ill.: Charles C Thomas, 1934. Price, $2.50.

Conception Period of Women. By DR. KYUSAKU OGINO, Head of the Gynecological Section of Takeyama Hospital, Niigata, Japan (Nippon). English Translation by DR. YONEZ MIYAGAWA, Director of Government Institute for Infectious Diseases, Tokyo Imperial University, Hongooku, Tokyo, Japan. Pp. 94; 22 tables. Harrisburg: Medical Arts Publishing Company, 1934. Price, $1.00.

Cataract. Its Etiology and Treatment. By CLYDE A. CLAPP, M.D., F.A.C.S., Associate Professor of Ophthalmology, Johns Hopkins University; Professor of Ophthalmology, University of Maryland, etc. Pp. 254; 92 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $4.00.

Synopsis of Genitourinary Diseases. By AUSTIN I. DODSON, M.D., F.A.C.S., Richmond, Virginia. Pp. 275; 111 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $3.00.

Studies in Blood Formation. By T. D. POWER, M.D., M.R.C.P., D.P.H., D.P.M., Deputy Medical Superintendent, Brentwood Mental Hospital. Pp. 124; 25 illustrations. London: J. and A. Churchill, Ltd., 1934. Price, 8s. 6d.

The Doctor in History. By HOWARD W. HAGGARD, Associate Professor of Applied Physiology in Yale University. Pp. 408; illustrated. New Haven: Yale University Press, 1934. Price, $3.75.

Krebs im Lichte biologischer und vergleichend anatomischer Forschung. By MED. DR. JOSEF L. HARTSCHNEIDER, Lintz a. d. Donau. Volume 2, No. 1. Albuminoide, Schilddrüse, Kropf, Hypophyse, Eierstock, Adenosis. Pp. 94; 19 illustrations. Leipzig: Franz Deuticke, 1934. Price, Rm. 5, S. 7.50.

The Patient and the Weather. Vol. 3 Mental and Nervous Diseases. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 375, lithoprinted; 192 illustrations. Ann Arbor: Edward Brothers, Inc., 1934. Price, $5.00.

The Cyclopedia of Medicine, Volumes 11 and 12. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. Vol. 11, 1111; Vol. 12, 1004. Illustrated with half-tone and line engravings, also full page color plates. Philadelphia: F. A. Davis Company, 1934. Price, $120.00 set. (Review, p. 862.)

NEW EDITIONS.

Rules for Recovery from Pulmonary Tuberculosis. A Layman's Handbook of Treatment. By LAWRASON BROWN, M.D., Saranac Lake, N. Y. Pp. 275. Sixth edition thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $1.75.

Applied Anatomy. By GWILYM G. DAVIS, M.D., Late Professor of Orthopedic Surgery and Associate Professor of Applied Anatomy in the University of Pennsylvania. Pp. 717; 674 illustrations, many in colors by ERWIN F. FABER. Ninth Edition, reset, reillustrated and completely revised by GEORGE P. MULLER, M.D. Assisted by DRS. B. J. ALPERS, R. A. KIMBROUGH, JR., S. W. MOORHEAD, I. S. RAVDIN and S. D. WEEDER. Philadelphia: J. B. Lippincott Company, 1934. Price, $9.00.

Practical Obstetrics. By P. BROOKE BLAND, M.D., Professor of Obstetrics, and THADDEUS L. MONTGOMERY, M.D., Associate in Obstetrics, Jefferson Medical College, Philadelphia. Pp. 730; 516 illustrations, including 21 colored plates. Second edition. Philadelphia: F. A. Davis Company, 1934. Price, $8.00.

The evident need for a medium size volume on obstetrics is manifested in the early appearance of a second edition of this excellent textbook. The teaching is modern but conservative, and stress is laid upon the practical aspects of the subject, especially as regards hygiene and home obstetrics.

A Manual of the Practice of Medicine. By A. A. STEVENS, A.M., M.D., Honorary Consulting Physician to the Philadelphia General Hospital; Consulting Physician to St. Agnes Hospital, Philadelphia. Pp. 685; 15 figures. Thirteenth edition, revised. Philadelphia: W. B. Saunders Company, 1934. Price, $3.50.

That it has reached its thirteenth edition is the best evidence of the popularity of this excellent little manual.

Allergy and Applied Immunology. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 420; 23 illustrations, 36 tables and 18 charts. Second edition. St. Louis: The C. V. Mosby Company, 1934. Price, $5.00.

An excellent book for general practitioners, students, and patients. There has been added a very useful appendix with diet lists, recipes, food diaries, and the like.

Diabetic Manual for Patients. By HENRY J. JOHN, M.A., M.D., F.A.C.P., MAJ. M.R.C., Director of the Diabetic Department and Laboratories of The Cleveland Clinic. Pp. 232; 47 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1934. Price, $2.00.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
FRANKLIN G. EBAUGH, M.D.,
PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
AND
GEORGE JOHNSON, M.D.,
PROFESSOR OF NEUROPSYCHIATRY, LELAND STANFORD UNIVERSITY.

TRAUMA OF THE CENTRAL NERVOUS SYSTEM.

THE increasing frequency of injuries to the central nervous system associated as it is with the high speed of modern life has presented a most important problem in the practice of medicine. The mechanization of our daily life, both in transportation and in industry, has been attended by increasing hazards which have taken an unusual toll in injuries to the brain and spinal cord. That there should still be considerable difference of opinion in regard to the various features of this problem is not remarkable when we consider that the tremendous increase in the incidence of brain injuries has been paralleled by an equally tremendous change in the concepts of neuropathology, neurophysiology, neurosurgery, and psychobiology. This review will consider these various concepts.

Pathology.—Winkelman and Eckel[1] review the extensive literature in this field, especially during the early stages, and present the results of their own investigations. They report that the brain of the patient who dies hours after a severe head trauma often shows a subarachnoid hemorrhage with maceration of the brain on the under surface of the frontal and temporal lobes. They believe this to be due to the lack of an adequate water bed between these parts of the brain and the base of the skull. Gross hemorrhage in the brain substance is fairly common with contusion or maceration of the tissue in the immediate neighborhood. The hemorrhage, far more frequently than is thought, is due to *contre-coup*. Subdural bleeding is a less frequent finding and epidural hemorrhage comparatively rare. On section, aside from gross hemorrhages, contusion and maceration, intense congestion, edema and petechiæ are frequently encountered. The latter are frequently limited to the subcortical white matter as in various infections, intoxications and blood dyscrasias. The onset of edema increases the damage to the brain. In accord with Apfelbach, they do not find edema present

within the first several hours or after the third day. When edema does occur, there is interference with the blood supply to the brain with subsequent ischemic changes in the ganglion cells and areas of focal necrosis similar in every way to the areas resulting from obstruction to the minute bloodvessels from any cause (arteriosclerosis, severe infections and intoxications). The development of pial-cortical adhesions could be traced from the beginning as the result of subarachnoid hemorrhages and secondary reaction. There appeared to be convincing evidence in the brains of patients with severe head trauma, especially those in whom unconsciousness had been prolonged, that most of those patients have organic changes in the brain which explain the post-traumatic symptom complex usually characterized as "traumatic neurosis."

Rand and Courville,[2] have investigated the cellular reactions following injury. The microglia exhibit changes depending on the severity and age of the injury. Occurring soon after injury they show as vacuolization, mitotic and amitotic cell division, swelling of the major processes and transitional changes, including the formation of fat granule bodies. The authors agreed with the experimental observers[3] that the microglia exercise a phagocytic rôle, the activity of which is mainly focal, confined to the place of lesion. In contrast, the rôle of the oligodendroglia is usually general. The early changes are the acute, more or less uniform swelling in all portions of the brain and may occur promptly, observed for instance in a person killed outright. Of the classic neuroglia, they found that in the first few days following trauma, the astrocytes in the immediately adjacent area undergo regressive changes with the formation of ameboid-glia. In the zone nearest the point of injury, the cells undergo complete destruction. Beyond this zone, active proliferation takes place. Gliosis occurs only as a result of tissue destruction, consequently remains a purely local affair. From their studies, they express the belief that the remote clinical sequelæ of injuries are largely to be interpreted on the basis of focal and distant cortical injuries and not from generalized gliosis.

In the production of the cerebral damage by *contre-coup* injury, interesting observations have been made by Le Count and Apfelbach[4] and Vance.[5] They demonstrated that *contre-coup* lesions occur only when the patient's head is injured while in motion. In such circumstances, the brain lags behind and is most closely applied to the after-coming portion of the skull. The skull is flattened at the point of impact and the brain immediately beneath is directly injured by this local application of force. In addition, however, because the axis of the skull is abruptly shortened at right angles to the plane of impact and because the brain is most closely applied to the bone directly opposite the point of impact, the most severe injury occurs at this place.

The management of patients suffering from the immediate effects of cerebral trauma is dependent upon two principal views of intracranial pressure relationships. In the opinion of Russel,[6] "It is important to bear in mind that a degree of increase of intracranial pressure provides a powerful means of controlling hemorrhage from torn capillaries and veins. In this way cerebral edema may prevent hemorrhage and correspondingly, the artificial reduction of intracranial pressure may aggravate it." In Dandy's[7] opinion, also, the immediate effect of trauma to the brain is the same as in any other soft tissue, mainly

swelling due to hemorrhage and edema. Nature's method of combating this increased volume in the closed cranial cavity is to withdraw fluid from the ventricular and subarachnoid systems and send it into the blood. The evidence of the state of balance existing between this increasing pressure and Nature's efforts to compensate for it, is to be found in the clinical observation on (1) the state of consciousness, (2) restlessness, (3) involuntary micturition or defecation, (4) rate and quality of the pulse and (5) respirations, and (6) the temperature. Of these the state of consciousness is the most important of all objective data. If a patient is unconscious, he has intracranial pressure beyond a certain degree of compensation which may be considered the margin of safety. Likewise, restlessness, a labile and increasing pulse; rapid, shallow and irregular respiration and a temperature above 101.5° or 102° F., are signs indicative of a failing compensation in intracranial pressure relationships. In accord with this view, Dandy states that "the only treatment up to a certain point in acute injuries is absolute rest." If after a period of 5 to 6 hours, consciousness improves or remains unchanged and the other signs remain within the limits of compensation, recovery will probably be spontaneous. If after this arbitrary period coma deepens and other signs indicate a break in compensation, recovery is practically impossible except for constant relief of pressure which can be obtained only by a subtemporal decompression.

An opposing viewpoint is presented by Munro,[8] who cites the work of Cushing,[9] Forbes[10] and Forbes and Wolff.[11] They demonstrated that following a rise in intracranial pressure there is a slowing of the blood flow in and dilatation of the veins and arteries, the circulation being maintained (without increase in the systemic blood pressure) by a rise in pressure in the cerebral capillaries, arterioles and smaller arteries. Following a further rise in intracranial pressure, the cerebral circulation is then reëstablished. This compensation may occur by steps. Such slowing of the capillary circulation is equivalent to anoxemia applied to the tissues of the brain generally. Depending upon the degree and the length of time it is present, there is a proportional cellular destruction, petechial softening, edema, further stasis and stagnation and capillary hemorrhage. Small areas of destruction may coalesce into larger areas with further spreading edema and further rise in intracranial pressure. These and further observations show, in Munro's opinion, "that cerebral venous and capillary pressures are approximately equal to intracranial (cerebrospinal fluid) pressure and they rise and fall with it. This high intracranial pressure cannot cause hemostasis without causing anoxemia and necrosis of the brain. By the same token lowering a high intracranial pressure by lumbar puncture decreases venous bleeding, because the venous pressure falls with the lowering of the cerebrospinal fluid pressure. The venous pressure is high because the intracranial pressure is high. Arterial pressure is rarely a factor since it is not affected until the intracranial and cerebral venous pressures approach arterial diastolic pressure, *i. e.*, 900 to 1100 mm. of water. Obviously arterial bleeding can never be checked by increased intracranial pressure; capillary stasis and death would take place long before such an intracranial pressure (1600 to 2000 mm. of water) could act on the arterial stream."

In keeping with these views, the treatment of acute injury rests upon measures designed to reduce the intracranial pressure by the artificial reduction of brain volume and the removal of excess fluid. The fundamental treatment of the patients reported by Munro consisted of a combination of therapeutic dehydration and decompression by lumbar drainage. For dehydration, 50% glucose intravenously, repeated once or twice if necessary, and a saturated solution of magnesium sulphate by rectum, repeated every 3 or 4 hours for 3 or 4 doses, were the measures used. Repeated lumbar drainage checked by manometric readings provides a means of removing excess fluid and of measuring the effectiveness of the other procedures in the control of intracranial pressure. Dehydration is properly limited to cases of edema or to use as a preliminary emergency treatment in cases of contusion and laceration. Lumbar puncture is suitable, however, for all three types of uncomplicated brain injuries. The edema is relieved because, with the reduction of intracranial pressure to normal, the venous congestion is corrected and the reactivated circulation allows the partially damaged asphyxiated cells to recover as much as possible. The excess intracellular and perivascular fluid is then absorbed and the brain volume is thus returned to normal. In contusions and lacerations, the excess unabsorbed fluid is mechanically removed together with a small amount of free blood and the meningocytes, if the drainage be repeated often enough, are aided in the uncorking of the absorptive channels in the arachnoidal villi. In those cases that are not immediately fatal, this treatment is expected to cause a progressive improvement in the patient's signs and symptoms. If this does not occur and toxic dehydration and meningitis can be ruled out, exploratory bilateral temporal trephine is considered indicated. This serves to eliminate the possibility of sub- or extradural hemorrhage or of one of the rarer forms of brain injury.

Although Russel[6] contends that morphin is "useful and can apparently be given without danger," there is general agreement[7, 8] that its use is hazardous as it masks symptoms and tends toward respiratory depression. Also, the meager information given by the Roentgen rays in regard to the true condition of the patient rarely warrants the disturbance of the patient's rest to make these examinations.

In considering the late effects of head trauma there have been several contributions during the past year. Straus and Savitsky[12] in an extensive review direct attention to the organicity of the so-called post-concussion syndrome. They deplore the attitude of hostility evidenced by the general medical profession toward the patient who exhibits personality changes after head trauma. They emphasize the necessity of preserving objectivity and the spirit of clinical investigation in the cases of patients who present symptoms which are confusing in the picture of common syndromes. They direct attention to a scheme of procedure which utilizes modern methods of investigation in establishing the nature of post-traumatic reactions. Of first importance is a careful exhaustive neurologic examination. Recently so much stress has been put on psychologic and social factors in the nervous symptoms that adequate neurologic examination has been neglected. Attention to detail with especially complete investigation for slight defects which may indicate focal lesions will result in fewer reports of "negative

neurologic findings." Psychologic and psychiatric surveys should likewise be more complete than simply limited interviews. Careful studies of the conscious processes (the nature of the intellectual processes, the quality of the sensory experience and the status of the volitional tendencies), should be made. The ready fatigability, emotional lability, difficulty in thinking and mild symptoms of mental defects are recognized as early symptoms in such organic psychoses as early dementia paralytica, cerebral arteriosclerosis and brain tumor but are frequently ignored or attributed to simulation when observed as part of the post-traumatic reaction. The use of the special techniques developed in the psychologic laboratories by which memory, fatigability, learning ability, etc., are investigated, have proved helpful both diagnostically and in suggesting at times practical methods of rehabilitation. The commonly used intelligence test, the Binet-Simon, and the performance test are of value only if there is the control of a comparable test before the trauma. Too much emphasis has, they believe, been placed in the past upon the necessity of establishing the presence of intellectual defects in cases of organic disease of the brain. The defect may be largely limited to the affective sphere. There may be no difficulty in solving simple arithmetical problems, but there may be impairment of judgment in the sense of inability to evaluate ethical and social problems, lack of earnest relation to reality, loss of interest and initiative and other defects in the volitional processes.

The extensive distribution of the visual pathways through the brain has lead these authors to attach especial importance to complete ophthalmologic surveys. Extensive defects in the fields may exist without any complaint. Consequently, complete studies of the visual fields including the color fields must be carried out. The usual approximate tests made in office practice are not sufficient but complete study using a correct technique, proper illumination, tangent screen, etc., must be made. Ring scotomas have been frequently described after head injury and the suggestion is made that these may be due to the fatigability which runs through the whole clinical picture of the postconcussion state.

The frequency of dizziness as a complaint indicates the need of a thorough study of the vestibular and auditory functions. Lithicun and Rand[13] found abnormal responses to vestibular tests in all of 36 patients who complained of post-traumatic dizziness. Five of these patients were neurologically normal. By using the audiometer, Groves[14] found some degree of deafness in 31 of 42 patients with head injuries. Twelve of the patients might easily have passed for persons with normal hearing. These patients showed so called patchy tone gaps.

The use of encephalography is advocated by Straus and Savitsky as well as by others[15] as giving definite information of changes in the brain. Despite the absence of normal controls, the distortions of the ventricular system, basal cisterns and cortical markings are such that if adequate care has been taken to follow a uniform technique in the encephalographic procedure, much valuable information may be secured in regard to the site of lesions. Penfield directs attention to the therapeutic value of encephalography in post-traumatic headaches. His explanation is that the air serves to break up adhesions in the pia-arachnoid.

In evaluating the evidence of organic injury, Kennedy[15] gives the following criteria:

A. *Absolute Criteria:* 1, Roentgen evidence—skull fracture; 2, bloody spinal fluid; 3, bleeding from the orifices, especially from the ears; 4, focal cerebral palsies.

B. *Presumptive Criteria in the Order of Their Importance:* 5, Convulsive states proved to be post-traumatic; 6, ventricular distortions proved to be post-traumatic; 7, history of prolonged unconsciousness; 8, history of adequate trauma with expecial consideration of the occurrence of vomiting following the injury. These units are in a real sense measurable, he states, and are instruments for establishing the fact of brain injury. The first four units, together with Nos. 7 and 8, can be determined with accuracy. Convulsive states are often complained of but are not always readily seen. One may satisfy oneself of their reality by provoking an attack in many instances by cocain or hyperventilation; this evidence is of value when positive. Headaches and dizziness are well nigh imponderable factors after head injury. However, if they persist for more than 4 months in a man under 60, ununited to any of the first seven premises of brain injury they are to be regarded as suggested neuroses unfounded in structural change.

The symptomatology of head injuries has been studied more carefully from a neurologic than from a psychiatric point of view. Since the important paper by Meyer[17] there have been few detailed psychiatric studies. Schilder[18] examined 35 cases suffering from severe head injuries utilizing newer psychologic apparatus in an effort to correlate symptomatology and psychophysiologic mechanisms. He emphasizes the significance of extensive periventricular hemorrhage in the final elaboration of the disturbance in the memory, in the judgment and in the Korsakow's pictures. Straus and Savitsky[19] distinguish three types of psychogenic disturbances following trauma, the Terror neuroses, Psychoneurosis precipitated by trauma, and Secondary psychologic elaborations. The terror neurosis is the direct reaction to the sudden threat to ego integrity, the psychosomatic response to the overwhelming of the individual by impending calamity. It is not often seen in head injuries for the automobile and industrial injuries happen so suddenly that there is little time for the patient to be impressed by the terrifying prospect of impending destructions. The psychoneurotic syndromes usually appear immediately after the injury and their further course hardly differs from that of the usual psychoneurotic except for the presence of the compensation problem. The secondary psychologic elaborations are frequent. They appear superimposed on organic sequelæ and usually disappear after satisfactory financial settlements even though the organic sequelæ persist.

Hall and Mackay[20] believe that the post-traumatic neuroses do not differ in any essential way from most other non-traumatic neuroses. The majority of these neuroses fall into one of three groups: Post-traumatic Neurasthenia, Post-traumatic Anxiety Neurosis and Post-traumatic Hysteria. They point out that there must be some pre-existing factor present to determine the development of the neurosis. The fact that great numbers of patients who have received the most severe injuries do not develop a neurosis, while in others the slightest injury suffices to precipitate a severe nervous state, suggests strongly

that people who develop post-traumatic neuroses already had the psychologic basis for the breakdown and that the injury served merely as a precipitant. Schaller and Somers[21] found that after recovery from a post-traumatic neurosis had begun a certain point was reached when recovery ceased and the patient remained at a standstill or retrogressed. It thus appeared that after the immediate illness had been alleviated, the untoward circumstances in connection with the injury adjusted, the fight for compensation ended, the repeated medical examinations stopped and the patient back at work, there still persisted a personality defect which rendered the patient subnormal. Treatment of the post-traumatic features according to Hall and Mackey centers around the establishment of a proper rapport with the patient, the settlement of compensation claims promptly and by a lump sum and the prompt vocational reëstablishment of the patient. Aside from these special features the treatment employs the same procedures indicated in the case of any psychoneurosis. GEORGE JOHNSON.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 15, 1934.

A Reconstruction of the Basal Ganglia of the Adult Human Brain.—W. H. F. ADDISON and DORIS ACORN FRASER (Laboratory of Anatomy, University of Pennsylvania). To understand thoroughly the significance of the basal ganglia it is necessary to know both the morphology of the nuclei of which they are composed and the connections of the nuclei to other regions of the brain. The anatomic investigation of this large mass of the brain has been relatively slight while the great

bulk of the literature has been contributed principally in the fields of neuropathology and clinical medicine. Because of the importance of the extrapyramidal system clinically it has seemed desirable to make a reconstruction of the corpus striatum and related parts based on the adult human brain. Series of sections were made of the central core of the brain at 50 μ both in a sagittal plane and in a plane at right angles to the midbrain. Projection drawings were then made, at a magnification of 5, of every eighth section. Wax plates were cut out according to these drawings and stacked to give a reconstruction at an enlargement of 5 in each dimension.

The reconstruction shows very well the shape and size of the striatum, the red nucleus, the substantia nigra and corpus Luysii. The pallidum was reconstructed also, but it is practically surrounded by the striatum and can only be seen from the medial view. The lateral part of the thalamus, where it did not overshadow any of the structures we were studying, was also reconstructed, as was the lateral part of the amygdaloid nucleus where it comes into close relation with the tail of the caudate. The rostral fusion of the caudate and putamen can be appreciated in this model, and the cellular bridges along the body and tail of the caudate which join with the putamen. Smaller cell bridges exist between the caudate and the globus pallidus and the close juxtaposition of these two nuclei is appreciated. The relationship between the head of the caudate and the anterior perforated space and the ventral surface of the brain is seen. A confluence exists between the tail of the caudate, the putamen and the amygdaloid. Tentative deliminations have had to be made awaiting silver material and further cell preparations. The reconstruction will serve as a starting point to study myelination and phylogeny.

The Basic Nitrogenous Extractives of Necturus Muscle.—D. Wright Wilson and William A. Wolff (Laboratory of Physiological Chemistry, University of Pennsylvania). The composition of muscle varies considerably among the different orders of animals. Creatin, carnosin, anserin and carnitin are found in the higher vertebrates and arginin and betain are found in the invertebrates. The isolation of extractives from the muscle of Amphibians has never been reported.

An aqueous protein-free extract of *Necturus* skeletal muscle was precipitated with phosphotungstic acid. The filtrate yielded creatin. The precipitate was fractionated with silver nitrate and barium hydroxid. Carnosin was isolated from the third silver precipitate and identified as the free base and as the characteristic copper salt. The fraction not precipitated by silver yielded trimethylamin oxid as a picrate. Betain and anserin were not obtained.

This is the first report of an isolation of trimethylamin oxid from a fresh water animal. It has previously been found in the muscles of salt water fish and in cephalopods but has never been found in fresh water fish. Its presence in the river crab has been suggested by an indirect quantitative study.

The Renal Excretion of Inulin, Creatinin and Xylose in Normal Dogs.—A. N. Richards, B. B. Westfall and Phyllis A. Bott (Laboratory of Pharmacology, University of Pennsylvania). The plasma clear-

ances of inulin and creatinin, simultaneously measured in normal dogs, were found to be of the same order of magnitude. The plasma clearance of xylose was found to be significantly less than that of inulin. These results harmonize with the view that in dogs the plasma clearance of creatinin is more nearly a true measure of glomerular filtration than is that of xylose.

The reasons for choosing inulin as the subject of study in these experiments were:

1. Its molecular weight is high and, compared with creatinin or xylose, its diffusibility is low.
2. It is not hydrolyzed in the animal body but, when injected intravenously, is excreted rapidly by the kidney, in high concentration and completely.
3. Its concentration in urine and plasma can be determined quantitatively by measurement of reducing power after hydrolysis by acid.
4. It is filterable through collodion membranes which are impermeable to protein and through the glomerular membranes of amphibia.
5. It is not excreted by the aglomerular kidney of the toadfish.

From these characteristics inulin might be expected to be filtered through the glomerulus, to be neither secreted nor actively reabsorbed by the tubule and to diffuse out of the tubule more slowly than xylose. The results do not disagree with this expectation.

The Renal Excretion of Creatinin and Certain Organic Compounds of Iodin.—E. M. Landis, K. A. Elsom and P. A. Bott (Laboratory of Pharmacology, University of Pennsylvania, and the Renal Clinic, University Hospital). The plasma clearances of Skiodan (mono-iodomethane sulphonate of sodium), Neoskiodan or Diodrast (3:5 diiodo-4-pyridon-N-acetic acid diethanolamine) and Hippuran (sodium orthoiodohippurate) were compared with that of creatinin.

In unanesthetized dogs Skiodan clearances were approximately equal to, or slightly lower than, the simultaneous creatinin clearances, regardless of the level of plasma Skiodan, within the limits studied. Neoskiodan clearances, on the contrary, ranged from 3.85 to 0.96 times the creatinin clearances. Identical with creatinin clearances when plasma Neoskiodan was high, they became several times greater than creatinin clearances as plasma Neoskiodan approached zero. Hippuran clearances ranged from 2.3 to 0.76 times the creatinin clearances and were similarly dependent upon the concentration of Hippuran in plasma, except that they became slightly, but definitely, lower than creatinin clearances when the concentration of plasma Hippuran was high.

In man the dosage of organic iodin was necessarily limited to amounts which could be administered with complete safety; the concentrations of organic iodin in human plasma were therefore much lower than in dog plasma. Human blood plasma was cleared of Skiodan and creatinin at approximately the same rate, the clearance ratios ranging from 1.13 to 0.85 even when the concentration of Skiodan in plasma was very low. The clearances of Neoskiodan and Hippuran, however, ranged from 1.5 to 6.8 times those of creatinin.

Changes in Duodenal Motility Associated with Gastric Peristalsis.—J. E. THOMAS and J. O. CRIDER (Laboratory of Physiology, Jefferson Medical College). A study by graphic methods of gastric and duodenal activity during digestion in unanesthetized dogs confirms the observations of others on anesthetized animals that rhythmic activity in the duodenum is regularly diminished or absent while a gastric peristaltic wave is approaching the pylorus and increased at the end of the antral cycle.

The gastric peristaltic wave may pass over the pylorus to the duodenum but the following new facts do not support this interpretation: (1) The activity of the duodenum at the end of the antral cycle does not conform to the usual description of intestinal peristalsis. (2) Its rate of transmission in the duodenum (10 cm. per second) is too fast for peristalsis but agrees with the rate of conduction of descending inhibition. (3) The gastric influence appears to diminish duodenal activity instead of increasing it.

The authors prefer to attribute the result to inhibition advancing ahead of the antral wave. The activity at the end of the antral cycle may be independent activity characteristic of the uninhibited duodenum.

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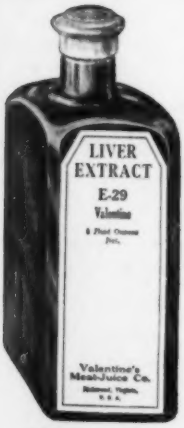

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Of further interest is the paper by Ruffin and Smith entitled, "The Treatment of Pellagra with Certain Preparations of Liver" in the April, 1934, issue of *This Journal.*

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IN ORDER to determine the comparative vitamin A value of the cod liver oil which forms 30% by volume of MALTINE WITH COD LIVER OIL, and the vitamin A value of plain cod liver oil, extensive experiments with animals have been conducted in the laboratory of one of the country's leading universities.

The results of these experiments confirm in every particular the conclusions drawn from previous tests, that the vitamin A value of cod liver oil as it exists in the MALTINE product is appreciably enhanced. The latest tests show that this enhancement amounts to a twofold increase.

Test animals in Group 1 were fed 4.0 mgs. of Maltine With Cod Liver Oil (containing 0.8948 mgs. of cod liver oil) and developed a highly satisfactory rate of growth. An equivalent amount of plain cod liver oil (0.8948 mgs.) fed to animals in Group 2 failed to produce satisfactory growth. It was not until twice this amount of plain cod liver oil—or 1.7896 mgs. —was fed to Group 3 that the growth rate approximated that of Group 1, in which half the quantity of oil was fed in the form of Maltine With Cod Liver Oil. It is evident from these tests that the vitamin A value of a given amount of cod liver oil as it exists in the Maltine product may be at least *twice* that afforded by the same amount of oil administered as plain cod liver oil.

Maltine With Cod Liver Oil is biologically standardized and *guaranteed* to contain vitamins A, B, D and G. Administered with either orange or tomato juice, vitamin C is provided. Biological report sent to physicians and institutions on request. Address The Maltine Company, 30 Vesey Street, New York, N. Y.

This Trade-mark identifies the Only Genuine

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We do our part

Maltine

Reg. U. S. Pat. Off.

Accepted American Medical Association

WITH COD LIVER OIL—INTRODUCED IN 1875

MALTINE WITH COD LIVER OIL AND IRON IODIDE is also available. This is identical with MALTINE WITH COD LIVER OIL except that it contains two grains of freshly prepared iron iodide to each fluid ounce.